FEDERAL TRADE COMMISSION

ECONOMIC REPORT ON ANTIBIOTICS MANUFACTURE

JUNE 1958

FEDERAL TRADE COMMISSION

ECONOMIC REPORT

ON

ANTIBIOTICS MANUFACTURE

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FEDERAL TRADE COMMISSION

LETTER OF TRANSMITTAL

FEDERAL TRADE COMMISSION,
June 27, 1958.

SIR: I have the honor to transmit herewith the economic study of the Federal Trade Commission entitled "Economic Report on Antibiotics Manufacture."

A limited number of copies of the report is being printed by the Federal Trade Commission.

By direction of the Commission.

Sincerely yours,

JOHN W. GWYNNE,
Chairman.

The President of the Senate,
Washington, D. C.

The Speaker of the House of Representatives,
Washington, D. C.

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INTRODUCTION AND SUMMARY

Introduction

Origin and scope of study

Because of the great public interest in the availability of medicines at reasonable prices, and the substantial share which antibiotics are taking in consumer expenditures for drugs and medicines, the Federal Trade Commission on July 22, 1953, adopted a resolution authorizing and directing an inquiry into the organization and operation of the antibiotics branch of the ethical drug industry.

Steps were taken to initiate the study, but pressure of other investigations prevented the assignment of sufficient personnel to carry it beyond the planning stage until 1956, when the staff of the Bureau of Economics could return to this problem.

An amended resolution was adopted by the Commission on July 13, 1956, to renew the authorization for the inquiry. The text of the amended resolution follows:

FEDERAL TRADE COMMISSION

AMENDED RESOLUTION

Report on Antibiotic Drug Industry

Whereas the commercial manufacture of antibiotic substances in the United States has within less than a decade, developed into one of the major branches of the ethical drug industry, and has come to be an important source of newly discovered food and feed supplements; and

Whereas the general public contributed largely to the establishment of an antibiotics industry in the United States through Federal Government promotion of research by which methods of producing antibiotics were developed, and through Government incentive to stimulate commercial production of penicillin; and

Whereas the industry is important to the public health and welfare, since antibiotic substances are more potent against a variety of diseases than any drugs previously known, and other substances produced by antibiotic manufacturers have unique value as food and feed supplements in human and animal nutrition, while new potentialities are still being revealed; and

Whereas there is a broad public interest in the availability at reasonable prices of the antibiotic drugs, as well as in continuing research and continuing incentives for the discovery and development of new uses and new antibiotics under the private enterprise system; and

Whereas it appears to the Commission that, for the reasons stated herein, and for the purposes set forth in Section 6 of the Federal Trade Commission Act, an investigation of the antibioties industry by the Federal Trade Commission would be in the public interest: Now, therefore, be it

Resolved, That the Commission, in the exercise of the powers vested in it by Sections 6 and 9 of the Federal Trade Commission Act, and with the aid of any and all powers conferred upon it by law and any and all compulsory processes available to it, do forthwith proceed to investigate, for the reasons and purposes stated herein the organization, business, conduct, practices, and management of corporations engaged in the production, sale or distribution of antibiotic drugs in commerce, as commerce is defined in the Federal Trade Commission Act, and the relations of these corporations to each other and to other corporations, and to individuals, associations and partnerships.

By direction of the Commission.

(Signed) ROBERT M. PARRISH,
Secretary.

JULY 13, 1956.

This study is concerned primarily with the use of antibiotics as ethical drugs, but some of their other applications, particularly in animal feeds, are sufficiently important to warrant consideration.

For several reasons, one of which was the limitation of funds, no study was made of the distribution of antibiotics to consumers through drugstores, hospitals, or other channels.

Two requests for company data

Immediately following the adoption of the new resolution, a data request was sent to the principal companies which were then, or had been, engaged in the manufacture of antibiotics. The questionnaire, which appears as appendix I, exhibit 1, required data on production, sales, prices, and patents. In May 1957 the same companies were presented with a request for data on costs and profits of antibiotics operations, as well as for additional data on production, sales and prices (appendix I, exhibit 2).

This report is based upon responses of the companies to the two data requests and upon published materials and governmental records relating to the industry.

The closing date for most statistics used in the report is the end of 1956. There have been changes since that time, as is naturally the case in a developing industry, but these changes have not affected the basic structure and functioning of the industry.

Principal antibiotic products and their manufacturers

"Antibiotics" and "antibiotic substances," as the terms are used in this report, mean chemical substances produced by a micro-organism, or identical substances produced by chemical synthesis, which have the capacity to inhibit the growth of other micro-organisms or to destroy them.

Penicillin, the first important antibiotic substance, was marketed in the form of various chemical salts.[1] The older salts, still made in

[1] A salt is defined technically as "any of a class of compounds formed when the acid hydrogen of an acid is partly or wholly replaced by a metal or a metal-like radical."

large quantities, are sodium, potassium, and procaine penicillin. In this report they are normally referred to by their generic names only, although in the market they are sold under many trademarks. The manufacturers of one or more of these salts in 1956 were: Abbott Laboratories; American Home Products Corporation (Wyeth Laboratories Inc.); Bristol-Myers Company (Bristol Laboratories Inc.); Eli Lilly & Company; Merck & Co., Inc.; Olin Mathieson Chemical Corporation (E. R. Squibb & Sons Division); Chas. Pfizer & Co., Inc.; and The Upjohn Company.

Streptomycin and dihydrostreptomycin were the next antibiotics to be introduced. They were discovered in 1943 and 1945, respectively. In 1956 they were made by Lilly, Merck, Olin Mathieson, Pfizer, and American Cyanamid Company (principally in its Lederle Laboratories Division). They may be marketed under their generic names, but trade names are often used, especially when these substances are marketed in combinations with other antibiotics.

Another important group comprises the "broad spectrum" antibiotics—so called because of the wider range of micro-organisms which they will destroy or whose growth they will inhibit. They are sold by the following companies and under the following trademarks:

Generic name	Trademark	Seller
Chloramphenicol	Chloromycetin	Parke, Davis & Co.
Chlortetracycline	Aureomycin	Lederle.
Oxytetracycline	Terramycin	Pfizer.
Tetracycline	Achromycin	Lederle.
	Polycycline	Bristol.
	Tetracyn	Pfizer.
	Steclin	Squibb.
	Panmycin	Upjohn.

In recent years new chemical salts of penicillin have been introduced, such as—

Generic name	Trademark	Seller
Benzathine penicillin	Neolin	Lilly.
	Permapen	Pfizer.
	Bicillin	Wyeth.
Phenoxymethyl penicillin (commonly called penicillin V).	V-Cillin	Lilly.
	Pen Vee	Wyeth.
Hydrabamine penicillin	Compocillin	Abbott.

Two other important antibiotics, the trademarks under which they are sold, and the names of their sellers, are listed herewith:

Generic name	Trademark	Seller
Erythromycin	Erythrocin	Abbott.
	Ilotycin	Lilly.
	(generic name used)	Upjohn.
Novobiocin	Albamycin	Upjohn.
	Cathomycin	Merck.

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Eleven kinds of penicillin and 18 other antibiotic substances were produced in 1956, of which 6 penicillins and 8 others have been listed above. The most important of those not listed were neomycin, oleandomycin, bacitracin, and nystatin, which accounted in 1956 for 6 percent of total sales. The 1956 antibiotics operations of two manufacturers, Commercial Solvents Corporation and S. B. Penick & Company, were confined to the minor products.

Most of these antibiotics are also marketed in combinations with other antibiotics under many different trademarks and trade names. For example, Bristol Laboratories, 1 of the 4 companies licensed to make benzathine penicillin, sells it only in combination with potassium and procaine penicillin, under the trademark Panbiotic. Combinations are rarely mentioned in this report.

Antibiotics of medicinal grade may be sold by original manufacturers either in "bulk" or in "dosage forms" (preparations ready for use by patients) bearing the label of the original maker. "Bulk" sales are commonly defined to include unlabeled dosage forms. The older salts of penicillin, streptomycin, and dihydrostreptomycin are sold in substantial quantities in bulk for packaging and labeling by others. Some of the newer products, such as tetracycline, are also sold in bulk under the terms of patent licenses.

Dosage forms fall into three classes: (*a*) "oral" forms such as tablets, capsules, and liquid suspensions, which are administered through the digestive tract; (*b*) those administered by injection and called by doctors "parenteral forms," which may be in solution, or in powder form with instructions on the container for adding a diluent to produce a suspension; and (*c*) "topical" forms such as ointments, lozenges, and powders, for external application at the site of the infection. There will be little reference to topical forms in this report.

Summary by Chapters

The following summary of the report covers the chapters (and any appendixes pertaining to them) in their order.

1. Origin of the industry

Penicillin, the first useful antibiotic, was discovered in England by Alexander Fleming in 1928, and its ability to eliminate disease-causing bacteria under test-tube conditions (more precisely: "in vitro") was noted. Not until 1939–41 was evidence provided by Howard W. Florey and Ernst B. Chain at Oxford University that penicillin could operate effectively against bacteria in laboratory ani-

mals and in persons.[2] Dr. Florey brought his findings to the United States in 1941 and stimulated interest in the potential usefulness of the new drug for the Armed Forces.

Research work on penicillin, already in progress at Columbia University and the Mayo Clinic, was now undertaken at the Department of Agriculture's Northern Regional Research Laboratory in Peoria, Ill. An Agriculture research team had previously worked out an improvement in the deep-vat fermentation process which made possible its application to antibiotics. To this was now added the discovery that corn steep liquor could be used as a nutrient medium in the fermentation process. These two contributions of Department of Agriculture scientists were significant in making volume production of penicillin possible.

The United States Government organized the whole wartime research and production effort, beginning in 1941, through the Office of Scientific Research and Development and the War Production Board. Difficult problems in producing penicillin had first to be solved. Approximately 20 pharmaceutical companies were authorized to enter the business, and most of them did get into production. Before the war ended, military needs had been met, and the drug was being made available in small quantities for civilian use.

One feature of the wartime program was research into the chemical structure and synthesis of penicillin, under contract with the Office of Scientific Research and Development, by several universities, the Department of Agriculture, and (without compensation) ten pharmaceutical companies. In order to speed the research and interchange of results, the Office negotiated a plan for allocation of any resulting patent rights; but few of the patents actually issued were to prove important.

Although synthesis of pencillin on a commercial scale was not achieved, the fermentation process became highly effective. In 1943 the Peoria group found a penicillin mold which increased the yield to about 100 times that of the original Fleming mold. This new mold was sent to the Carnegie Institution, which bombarded it with X-rays. A mutant strain was developed which increased the productivity of the Peoria mold about five times. Later, University of Wisconsin geneticists, using ultraviolet-ray bombardment, increased still further the productivity of this strain.

By 1945 a new and dynamic branch of the ethical drug segment of the pharmaceutical industry had emerged as a result of wartime

[2] Drs. Fleming, Florey, and Chain were awarded the Nobel Prize in Medicine and Physiology in 1945. In 1952 Dr. Selman A. Waksman was awarded this prize for the discovery of the second important antibiotic, streptomycin.

needs and of public and private cooperation in the organization of production and in research. At the same time the discovery of penicillin had given the impetus to a whole new area of study of micro-organisms, the boundaries of which are still being extended.

2. The influence of national defense on the development of the industry

In addition to the purchase of current production for the American and allied armed forces after 1943, Government funds stimulated the wartime development of penicillin through several channels.

Penicillin for medical testing purposes was supplied by the companies commencing late in 1941, and beginning in February 1943 payments totaling $2 million were made for these supplies. The small quantities so obtained made it possible to carry on extensive penicillin research. Contracts were concluded with many educational institutions and hospitals for specific projects. The known cost to the Government of subsidizing wartime research was approximately $2.8 million.

The first penicillin made in the United States was in hospitals, laboratories, and pilot plants. By 1943 enough had been learned to make plant construction possible. The Government built 6 production units at a cost of about $7.6 million, and the companies operating 2 of the plants added nearly $2.9 million in packaging and power facilities. After the war these plants were sold to the companies for a total of almost $3.4 million. The 44-percent recovery on the Government's investment was very close to the 45-percent recovery from the disposal of wartime Government-built plants in all industries. Counting four plants built for other wartime purposes but bought by antibiotics companies after the war, this industry's average payment to the Government did come to 45 percent of original cost.

The remaining 16 wartime antibiotics plants were financed by private industry, their total cost plus the private contribution to the first 6 plants being $22.6 million. Of this amount, $14.5 million, or approximately 64 percent, was approved for accelerated amortization under the Federal income tax. This permitted the companies to deduct their investment from taxable earnings over a 5-year period instead of the 12 to 15 years usually required for chemical manufacturing plants. Rapid amortization was a regular feature of the overall wartime program for stimulating expansion of defense industries.

Toward the end of the war and during the years following, additional antibiotics and new forms of the earlier antibiotics began to emerge from the research laboratories. Meanwhile, demand grew steadily as the uses of antibiotics were enlarged through clinical testing. The industry met the growing demand by expanding its

capacity and replacing the early flask-type production units with deep-vat fermentation equipment. Efforts were made to satisfy some of the foreign demand as well, at first through exports of penicillin under lend-lease and as relief to devastated countries. Later, penicillin production units were also sent to Europe.

The Korean war brought another major advance to antibiotics production. Under "Expansion Goal No. 129" (penicillin), industry expenditures of $110.3 million were approved, to expand capacity of the existing plants. On $62.8 million, or 57 percent of this $110.3 million, the accelerated 5-year amortization was granted.

An original production capacity goal of 3.6 billion international units of penicillin annually was set by the War Production Board during World War II. The goal at the time of the Korean war was 600 billion units. The plant expansion then and in the following years brought capacity to approximately 800 billion units at the end of 1956, as against 1956 production of about 560 billion units. For streptomycin and dihydrostreptomycin, two other important antibiotic substances developed during and shortly after World War II, the percentage of reserve capacity was about as great. In the newer antibiotics it was still larger.

The supply and potential supply of antibiotics appear to be substantial. Also, Government stocks have been established for civil defense and for military uses. In the event of a national emergency, these stocks would be available, and production could be stepped up to capacity.

3. Antibiotics production and manufacturers

Most chemical materials used in the production of antibiotics are purchased by the manufacturers, but a few firms produce some of them.

All principal manufacturers engage in the finishing and packaging of dosage forms from their bulk product. On the older salts of penicillin, these dosage forms come into competition with those of packaging firms—of which 45 were listed in the Drug Topics Red Book in 1956—which purchase their bulk product from these same manufacturers.

Between 1948 and 1956 total output increased from 240,000 to 3,081,000 pounds. Penicillin accounted for 65 percent of the total in 1948 and 34 percent in 1956. Streptomycin accounted for 34 percent and 5 percent in the 2 years, and dihydrostreptomycin for 1 and 16 percent. The first broad spectrum antibiotic was introduced in December 1948. In 1956 the 4 drugs now in the broad spectrum group accounted for 39 percent of total antibiotics production. More than half of this broad spectrum production, however, went into animal

feed supplements. The remaining antibiotics in 1956 consisted of erythromycin, 2 percent of the total; bacitracin, nystatin, and novobiocin, 2 percent when taken together; and various minor products, 2 percent.

Seventeen salts of penicillin and 22 other antibiotic substances have been produced at one time or another since 1948. Eleven penicillins and 18 other substances were being produced in 1956. Of this number, four penicillins and four other substances were introduced in 1956.

Due to price differences, antibiotics rank in dollar sales in a different order than in physical output. Counting only sales from the manufacturers' own production, which were approximately 90 percent of total sales in 1956, dollar totals came to $165 million for the broad spectrum antibiotics, $67 million for penicillin, $24 million for streptomycin and dihydrostreptomycin, $18 million for erythromycin, and $27 million for all others.

The peak year of manufacturers' dollar sales was 1951. Between 1951 and 1956 aggregate production of antibiotic substances doubled, but total dollar sales decreased. This was largely caused by falling prices for the older antibiotics and the development of new, non-medical uses at lower prices for both older and newer antibiotics. Seventy-two percent of volume of antibiotics production in 1956 was of medicinal grade, and 27 to 28 percent of animal feed supplement grade, while the remainder went for such other uses as crop spraying and food preservation. The total value of medicinal grade sales from the companies' own production was $273 million in 1956, and that of other grades was $28 million.

The nonmedicinal grades are generally sold in bulk containers at lower prices. The average sales value at the manufacturing level for chlortetracycline, which accounted for almost half of all animal feed sales in 1956, was $43 a pound when sold for this use. It was $259, or 6 times as much, in the medicinal grades.

No company in the industry started as a manufacturer of antibiotics, and all make other pharmaceutical products as well. Seven of the manufacturers were founded before 1900; 5 of these are still primarily or solely pharmaceutical manufacturers, while 2 have been absorbed into diversified corporations with important nonpharmaceutical interests—Wyeth Chemical Company, into American Home Products Corporation, and E. R. Squibb & Sons, Inc., into Olin Mathieson Chemical Corporation. Two of the other five manufacturers (those entering pharmaceutical production after 1900) are primarily or solely engaged in the pharmaceutical business, while 3 are connected with diversified companies. These three are the Lederle Laboratories Division of American Cyanamid Company; the Bristol Laboratories Inc., subsidiary of Bristol-Myers Company; and the ethical drug operation of Commercial Solvents Corporation.

Eleven of the twelve producers were in the wartime penicillin program. S. B. Penick & Co. began antibiotics manufacture in 1949. Of the other known wartime producers, 2 dropped out at the end of the war and 3 others later. Two firms entered the industry after the war, but then withdrew.

Approximately half of the total antibiotics volume in 1956 was produced by two companies: Pfizer and American Cyanamid, with 26 and 23 percent, respectively. For penicillin alone, Olin Mathieson, Merck, Lilly, and Pfizer accounted for 82 percent of output. The trends in concentration as measured by dollar sales are reviewed briefly in chapter VII.

In the first years of the industry, all its members manufactured penicillin. Two of the early penicillin salts, potassium and procaine, which were made in 1949 by 13 and 14 companies, respectively, were still made by 7 in 1956. Streptomycin and dihydrostreptomycin were made in 1949 by 8 and 7 companies, respectively, and in 1956 both products were made by 5.

Since the research work of the companies began to yield results in the middle and late 1940's, company specialties have played a larger role. In 1956 Pfizer was producing 14 antibiotics, Merck, 9, and 4 other companies 5 to 7 each. Seventeen of the twenty-nine antibiotic substances manufactured in 1956 were the product of a single company, 4 others of only 2 companies, and 2 others of 3 companies. It should be noted that the manufacturer of 8 of the 17 "exclusives" was not the patentee itself, but a licensee; these 8, however, were in no instance leaders in volume production or dollar sales. Statements by several of the antibiotics companies have emphasized the greater profitability of product specialties as against that of products which a number of other producers also offer.

In only four instances was the identical antibiotic the leading gross revenue producer among a company's antibiotic products in both 1950 and 1956. These were dihydrostreptomycin for Merck; chloramphenicol for Parke, Davis; oxytetracycline for Pfizer; and procaine penicillin for Squibb. In 1950 procaine penicillin had been the leading antibiotic product of eight other companies as well. The industry's greatest revenue producer in 1956 was tetracycline, which alone accounted for 24 percent of total dollar sales from manufacturers' own production. It was the leading antibiotic product of American Cyanamid and Bristol, and an important product of Pfizer.

In 1956 manufacturing or packaging plants of the 12 producing companies were located in 11 States. There were 11 manufacturing plants and 15 packaging plants in the Eastern States of Connecticut, New Jersey, New York, Pennsylvania, Virginia, and West Virginia; and 8 manufacturing and 10 packaging plants in the Midwestern

States of Illinois, Indiana, Iowa, Michigan, and Missouri. Abbott Laboratories, Eli Lilly & Co., Parke, Davis & Co., and The Upjohn Co. comprise what has been called the midwestern group. The Missouri and Iowa plants are packaging facilities owned by eastern companies.

Ten of the twelve manufacturing companies reported the establishment of foreign facilities between 1950 and 1956. They reported an increase in the number of their manufacturing plants abroad from 4 to 19, and of their packaging facilities from 25 to 77. In 1956 Parke, Davis had 9 manufacturing and 13 packaging units; none of the other companies had more than 12 facilities. The plants are in 22 countries, and show various degrees of ownership and control by the American manufacturers. The manufacturers have also concluded a number of contracts to provide technological information and assistance to foreign-owned manufacturing enterprises.

Nineteen companies now or formerly in the industry reported having spent $270 million for new domestic antibiotics plant and equipment from 1943 through 1956. More than half—$151 million or an average of $50 million a year—was invested during the 3 years of the Korean expansion program, 1951–53. Another $92 million, averaging $15 million a year, was invested in the interwar years 1946–50, and in 1954 when the Korean program was being completed. Only $27 million, or an average of $5 million a year, was invested in the other 5 years tabulated.

In the period 1950–56, the ratio of plant and equipment expenditures to sales averaged 9.0 percent for the antibiotics industry and 4.0 percent of all nondurable goods manufactured in the United States. After the spurt during the Korean war, the percentage in antibiotics dropped below the nondurable goods percentage.

Total employment in antibiotics operations of the manufacturing companies was around 35,000 in 1956. Based on returns from 5 companies, whose 1956 employment came to 17,000, 20 to 21 percent of 1956 employees were in manufacturing; 19 percent in "detailing" (i. e., selling); 14 percent in compounding and packaging; 8 to 9 percent in research and development; and 38 percent in administration, transportation, maintenance and other services. An increase of 23 percent in employment rolls of 4 companies between 1950 and 1956 was sufficient to permit an increase of approximately 300 percent in their aggregate production. Average pounds produced by these companies per worker engaged in manufacturing increased approximately 210 percent, and average pounds per packaging worker approximately 200 percent. Two factors probably explain these increases: the development of sales for nonmedicinal uses efficiently handled in bulk; and automation and improved technology, especially in packaging.

The greatest percentage increase in number of employees between 1950 and 1956 was in research and development. This is in line with the emphasis placed by the industry on the discovery of new products. Twenty-nine new antibiotic substances were introduced from 1949 through 1956, of which eight had been dropped before 1956. Several company reports have emphasized the importance to current sales and profits of products which did not exist a few years earlier.

4. The production process

The whole production operation takes a month or more. The key step is the fermentation process, during which the growth of the micro-organisms is stimulated by nutrients, aeration, and agitation in huge vats. Chloramphenical is an exception, being produced by chemical synthesis rather than fermentation.

The exact technical formula by which an individual manufacturer achieves an effective, stable, and large volume of output of a specific antibiotic substance is the manufacturer's trade secret. Culture strains of micro-organisms differ greatly in the amounts of antibiotics they are capable of producing, which makes selection of the micro-organism and improvement of culture strains important. Nutrients of various types and quantities are used, the chemicals employed in the process are not the same for different substances, and there is no standard formula for any single product. Improvements are constantly sought by the manufacturers.

Responding to intense efforts, the yield of antibiotic substances in bulk production has increased remarkably. One company reported that in 1945 a pound of penicillin required processing of 17,442 gallons of fermentation broth. In 1953, a pound of "antibiotics" (the kind not specified) was reputedly being obtained from 280 gallons of broth. In 1956, yields of the major antibiotics were reported by one writer to range from 1 to 5 grams per liter, which would be the same as 1 to 5 pounds for each 120 gallons of broth. Estimates of this kind are in terms of general ranges, since yields of particular substances are considered by the companies to be trade secrets. Yields differ from plant to plant and, in lesser degree, in the same plant as between different batches. Nevertheless, yields of the streptomycins and of those broad spectrum antibiotics which are produced by fermentation are likely to be of the same magnitude, since all are products of the *Streptomyces* group of micro-organisms. The yield of penicillin, which is produced by a mold, may average somewhat less.

Fermentation time as well as yield differs between plants and varies at times within the same plant. One authority holds that penicillin on the average requires the most time, followed in order by strepto-

mycin, chlortetracycline, and oxytetracycline. Another authority reverses the order between penicillin and streptomycin. Each, however, puts the fermentation time for the broad spectrum antibiotics below that of penicillin and streptomycin.

Yield and fermentation time are not the only influences on manufacturing cost. Fermentation time, for example, is only 5 to 15 percent of the total time required for production. Costs and efficiency of equipment, labor, power, and refrigeration are important; so are the amounts and costs of chemical and nutrient raw materials used. Raising the yield is sometimes uneconomical, because of the effect on raw material cost. Assuming all these other costs to be equal, however, the data on relative yields and fermentation times point to a slightly lower cost of production per pound for the newer broad spectrum antibiotics than for the older penicillins.

Under the Food, Drug, and Cosmetic Act, samples of each batch of seven antibiotic substances must be certified for potency and purity after tests by the Food and Drug Administration. Sample dosage forms must also be certified as meeting tests set out in its regulations. No new antibiotics have been added to the certification list since 1949, although derivatives of substances then listed require certification. New antibiotics, however, are authorized for sale only after they have met the Food and Drug Administration standards for new drugs.

Indicative of the increased "stability" being built into antibiotic substances is the lengthening period of potency for which many drugs are receiving approval. Antibiotics whose period was once set at 12 months are now certified for 24 to 60 months.

5. Marketing programs of antibiotics manufacturers

Makers of medicinal antibiotics direct their most intensive promotional efforts toward physicians, since, under the law, ethical drugs (a category which includes most of the antibiotic dosage forms outside of ointments, salves and lozenges) cannot be sold unless prescribed or dispensed by a physician. Manufacturers must at the same time persuade drugstores to keep their products in stock. A pharmacist whose stock on hand does not include a particular company's drug will, if a prescription calls for this drug by its generic name, fill it with any brand he has on hand, or, in the much more usual case where a trademarked drug is prescribed by name, ask the doctor's permission to make the necessary substitution.

Pharmaceutical manufacturers direct very little of their promotional efforts for ethical drugs to the general public, since consumers buy such drugs on prescription and do not make their own choices between them. The public is reached through the companies' institutional advertising and public relations programs.

Eight manufacturers reported to the Commission the following breakdown of their antibiotics selling and advertising expenses for 1956: salesmen's compensation, 44 percent; samples, 11 percent; advertising in periodicals, 10 percent; advertising by direct mail, 8 percent; other selling expenses, 27 percent. The sum of these expenses comprised 20.6 percent of net sales of the 8 companies, the range being from 9.6 to 30.7 percent. The average for 23 pharmaceutical companies covered in another survey was also 20.6 percent, the range being from 5.0 to 42.0 percent.

Selling representatives who call on doctors and druggists are known as detail men. They represent their firms on all pharmaceutical products, including antibiotics. Detail men have proved especially effective in introducing new products, although other means of promotion rival the effectiveness of detail men in retaining the loyalty of those physicians who already know the product. Ten leading antibiotics producers selling dosage forms reported to the Commission that they employed detail men; the number of detail men employed was about 7,000. According to one estimate, it would cost a million dollars to have detail men pay one visit a year to every practicing physician. The cost of making such visits several times a year to most physicians is too great for smaller firms, which do not have full ethical drug lines, to undertake.

Detailing played the leading role in the aggressive promotional campaigns that achieved rapid market acceptance for Achromycin and Terramycin, the trade names, respectively, of American Cyanamid for tetracycline and Chas. Pfizer & Co. for oxytetracycline. The first year's promotion budget for Achromycin was approximately $2.5 million, of which 42 percent was allocated to detailing, 35 percent to direct mail to physicians, 19 percent to medical journal advertising, and 4 percent to exhibits at medical meetings. During its 18-month Terramycin campaign, which also employed direct mail, journal advertising, and exhibits at hospitals, Pfizer increased its detailing force from 8 to 300 men.

The number of pages of antibiotics advertising placed in the Journal of the American Medical Association annually by 15 manufacturers ranged in the 1945–53 period from 32 pages (in 1949) to 157 (in 1951). A sharp increase in the number of pages began in 1954, and a total of 534 was reached in 1957. Before 1950 generic names such as penicillin or streptomycin were generally mentioned, but after that date the various trademarked, patented specialties were selected for emphasis. In 1957 approximately 275 of the 534 pages were devoted to tetracycline products as marketed under several trade names by five companies, and most of the remaining space was given to other broad spectrum antibiotics, erythromycin, and penicillin specialties

which offered a wider margin of profit than sodium, potassium and procaine penicillin. Copy which emphasized antibiotics ranged between 9 and 28 percent of these companies' total advertising in the Journal between 1946 and 1955—or a little more than 28 in 1955 if the space given to antibiotics in Pfizer's "Spectrum" were counted as "antibiotics" instead of "institutional" advertising. The percentage then increased to 35 in 1956 and 39 in 1957.

Free samples and direct mail are among the most important means of reaching physicians. When introducing its first broad spectrum antibiotic, Aureomycin, American Cyanamid shipped samples worth about $2 million to approximately 142,000 physicians. In the Achromycin campaign, a full list of the country's physicians received an average of two mailed items a week. Some of the items which go out by direct mail include expensively printed house magazines, "service material" such as anatomical drawings and printed prescription blanks, and, perhaps most frequently, brochures on the merits and use of particular products. Pharmaceutical houses also give wide circulation to reports of successful clinical studies made by their own scientists or by independent physicians at their request.

The promotion of antibiotics is conducted by the same methods as the promotion of other ethical drugs, and frequently in the same literature or on the same detail man's visits. Promotion generally emphasizes new drugs, for which the company is trying to build up a sufficient sales volume to warrant their production, and trademarked specialties, which the companies fear physicians might gradually cease prescribing unless reminded of their merits.

The channels of distribution are also the same for antibiotics and other ethical drug products. General-line drug wholesalers, and specialty-line drug wholesalers handling pharmaceuticals (numbering 392 and 461, respectively, in the 1954 Census of Business) supply more than half the average nonchain drugstore's prescription chemicals. Most of the retail druggists (44,511 in 1954) handle a full line of antibiotics, including parenteral forms sold to physicians, oral forms sold on prescription to customers, and topical forms that do not require a prescription. All antibiotic prescriptions are of the "dispensed" type which has largely replaced the old "compounded" type in the work of the pharmacist. Besides filling the prescriptions, the pharmacist plays an important role in supplying information to physicians.

An estimate in 1954 placed hospital purchases of antibiotics at about $67 million, comprising a substantial fraction of the antibiotics used. More than half of all hospitals have their own pharmacies. Small hospitals have no standardized system of charging patients for medication, but many of them fix the charge at double their own purchase price.

6. Pricing in the antibiotics industry

An account of the price history of the antibiotics industry must be preceded by a short survey of supply-and-demand factors. One of the most significant supply factors for each drug, in addition to the volume produced, is the number of companies competing in its manufacture and sale, and this is in turn often controlled by the patent situation. A sharp contrast is evident between the products which appeared before 1948—especially sodium, potassium, and procaine penicillin, streptomycin and dihydrostreptomycin—and the more recently introduced broad spectrum antibiotics, erythromycin and specialty penicillins. Patents for the former group were licensed to those interested. By 1949 the number of manufacturing companies had reached 13 for potassium and 14 for procaine penicillin, 8 for streptomycin, and 7 for for dihydrostreptomycin. Production of the recently patented products has been confined to one company or a very few at most.

The demand for antibiotic drugs is controlled by the incidence of the illnesses they are used to treat and by prevailing therapeutic practices. Whether an antibiotic will be used in a particular case is determined by the physician rather than the patient, and the choice is made on considerations of health rather than price. Even if the patient influenced the choice, it would hardly be on a price basis; if he places health considerations first, he simply follows his doctor's directions. A high price will do less to discourage demand than in many other industries. On the other hand, a physician is not likely to select a drug about which he knows little or whose maker he does not trust. Manufacturers, therefore, try to keep physicians familiar with their own names and the merits of their drugs. Where antibiotics sold by two or more companies are identical or closely substitutable, however, a lower price charged by one of them may influence the demand of distributors, hospitals, or even physicians.

Costs of research and clinical testing are ordinarily incurred before a new antibiotic is put on the market. A manufacturer's new drugs frequently compete with its old ones. A cost-saving factor in the production of a new drug is that the equipment used for the manufacture of the previous product can frequently be shifted to the new one.

The major manufacturers of bulk antibiotics prepare dosage forms; most of them also sell in bulk to independent firms which package dosage forms for resale under their own labels; and some make bulk sales to other manufacturers which to this extent themselves operate as packagers. In both types of bulk sale, the original manufacturer may also be selling in the dosage form market where its bulk customers are selling.

Part of this bulk sale to other manufacturers is according to term purchase contracts providing for purchase either of specific amounts, of minimum and maximum quantities, or of the buyer's purchase requirements or total requirements. These contracts have been made in at least the following products: penicillin, streptomycin and dihydrostreptomycin, chloramphenicol, and tetracycline. The prices named on the contracts carry sharp discounts below the prices paid by other bulk customers of the seller. On one penicillin contract used as an example, the price was 44 percent below the regularly quoted 400-vial price to such customers and 29 percent below the 100,000-vial price.

The provisions of the various types of term purchase contracts are not set out at length in the report, but one type which differs from the rest is the "distributor agreement." Under this, the supplier makes the other party its "nonexclusive selling agent," under the latter's labels but at prices which the supplier reserves the right to name. The margin stipulated for the "selling agent," in one streptomycin contract used as an example, began at 47.5 percent of the dosage form price in 1950 and, after 8 changes, had been raised to 63.9 percent (of a 40 percent lower dosage form price) at the end of 1954.

Dosage forms are sold to wholesalers, retailers, hospitals, and Government agencies. The wholesaler's margin varies between 15 and 21 percent of the price he charges the retailer. The margin between the published price to the retailer or hospital and the list price suggested by the manufacturer for resale to consumers is ordinarily 40 percent of the consumer price. When a minimum resale price is named by the manufacturer, it is almost always 10 percent below the listed retail price.

These published prices are modified in practice by a 2-percent cash discount and by quantity discounts offered by various manufacturers. In addition, shipment of "free goods"—i. e., of additional product up to as much as 50 percent of the original order—has at times been a competitive tactic in the penicillin and the streptomycin markets. Manufacturers normally allow their customers full credit for return of "expired" dosage forms which have lost their potency through passage of time. Finally, some manufacturers guarantee customers' floor stocks against price decline for a stated period after purchase. Pricing practices in antibiotics are similar to those employed in the distribution of other ethical drugs.

In 1945 amorphous sodium penicillin in bulk was quoted at $6,000 and in 1947 at $2,100 per billion units. Crystalline sodium penicillin, which replaced amorphous in 1947, was first quoted at $2,500, but by 1956 was as low as $50, from which it increased to approximately $63 late in 1956. Potassium and procaine pencillin were quoted at

$1,300 per billion units in1948, and as low as $34.50 for potassium in 1955 and $47.50 for procaine in 1956. By the end of 1956 potassium had increased to $57.50 and procaine to about the same figure.

These sharp decreases resulted from improvements in production efficiency and reductions in cost, the benefits of which were passed on to purchasers through active price competition of numerous manufacturers—as many as 14 in 1948 and 1949 and still 7 in 1956. The great expansion of capacity in the Korean war, and competition after 1948 from newer antibiotics substitutable in many respects for penicillin and which could be taken orally, put further pressure on penicillin prices. The most severe competitive price reductions occurred in 1949 and 1952, especially the latter year. Some of the prices actually charged were probably mere approximations of the quoted prices during times of sharp competition, because of discounts and special contractual arrangements.

The first price for penicillin dosage forms was $20 per 100,000 unit vial, paid by the Government in 1943. By August 1945, when flask-type production techniques had been replaced by deep-vat fermentation, the price is reported to have been below $1 per vial. In 1947 and 1948 the same dosage form was selling at 30 cents. Procaine penicillin, a much improved form, was introduced in 1948. A 3 million-unit vial, containing 10 doses, was offered to retailers by one of the companies in February 1948 at a price of $10. In October the price was reduced to $8 and in March 1949 to $6. Further decreases followed, the most severe price reductions being, as in bulk penicillin, in 1952. By 1956 the prices for a 3 million-unit vial of procaine penicillin in 3 commonly used forms were in the 56 to 66 cent range. From the 1943 price of the earliest type of penicillin to this 1956 price of procaine penicillin, there had been a 99.9-percent decline.

While major manufacturers were quoting procaine penicillin in aqueous suspension at 56 cents for 3 million units, 2 smaller packagers were quoting 45 and 50 cents while 4 were quoting from 68 cents to $1.34. A similar variation appears among prices of penicillin tablets. These, it should be noted, are usually sold to individuals whereas injection forms are sold only to doctors or hospitals. Tablets are both much less commonly used and much more expensive. The above-mentioned 56-cent price can be translated into 19 cents per gram, by using the 1,009-unit-per-milligram conversion factor employed by the Food and Drug Administration to translate chemically pure procaine penicillin into the metric system of weights. One hundred tablets of 100,000 units each were quoted by Lederle Laboratories in 1956 at a price equivalent to 63 cents per gram, as against 16 to 48 cents quoted by 4 smaller packagers. The same quantity of buffered potassium penicillin tablets (i. e., tablets to which a substance has been added to

prevent any great change in acidity or alkalinity in the patients digestive tract), converted at 1,595 units per milligram, was quoted at prices equivalent to 77 cents per gram by 5 major manufacturers and 27 to 45 cents by 4 packagers.

Price comparisions between different dosage forms of an antibiotic, or between penicillin and the other antibiotics, have been made on a per-gram basis. Although tablets and capsules of either penicilling or other antibiotics often carry more grams of potency than their labels declare, this raises all the per-gram price equivalents and does not significantly distort the comparisons. Two other limitations on per-gram comparisons should be noted: the costs of compounding, finishing and packaging large and small dosage forms differ; and physicians may prescribe tablets containing different numbers of milligrams for the same treatment depending on which antibiotic they have selected.

All published prices to retailers for potassium and procaine penicillin in tablet form were equivalent in 1956 to 91 cents per gram or less; all corresponding prices for the more recently patented antibiotics discussed in this chapter were $1.12 per gram or more. The largest package size of broad spectrum antibiotics contained 100 capsules of 250 milligrams each, quoted at $30.60 or the equivalent of $1.22 per gram. The smallest contained 25 capsules of 50 milligrams each, quoted at $1.89, or the equivalent of $1.51 per gram. Sellers of erythromycin have adopted the same prices for most dosage forms that already prevailed for the broad spectrum antibiotics. Benzathine penicillin and phenoxymethyl penicillin prices were in the same range. The two prices listed for benzathine were $6.67 for 36 tablets of 200,000 units, the equivalent of $1.12 per gram at the Food and Drug Administration conversion ratio of 1,211 units per milligram, and $10 for 100 tablets of 100,000 units, the equivalent of $1.21 per gram. One of the two sellers of phenoxymethyl penicillin (known also as penicillin V) listed its two 6.25-gram dosage forms at $7.50 and $9, equivalent to $1.20 and $1.44 per gram, and the other priced its 3.6 and 4.5-gram dosage forms at $4.32 and $6.48, respectively—equivalent to the same $1.20 and $1.44 per-gram prices.

The quoted prices of the broad spectrum antibiotics and erythromycin have not changed for several years; those of benzathine penicillin and phenoxymethyl penicillin have not changed since their introduction. None of these new products has been handled by outside packagers.

Bulk prices of streptomycin and dihydrostreptomycin have been identical with each other, and their trend has been similar to that of bulk penicillin prices. From 1946 to 1956, they dropped from $16 per gram to 7 cents per gram. Later in 1956, they increased to about 7.6

cents per gram. Term purchase contract prices were often lower than published bulk prices, touching 4.1 cents per gram early in 1956. Dosage form prices to private hospitals and retailers decreased in the same way: thus Merck & Co. was quoting $20 per gram in October 1945, $4 in April 1947, $1.60 in July 1948, and 36 cents from 1953 to 1956. In the intense price competition which has prevailed in the marketing of streptomycins, published prices have frequently been nominal, with transactions taking place at lower figures.

There are price differences among the major manufacturers and outside packagers of streptomycins. Quotations for 1 gram of powder in 1956 were 33 cents for 3 manufacturers; 36 cents for 2 others; and 29, 34, and 45 cents, respectively, for 3 packagers.

Price competition in the older penicillin and streptomycin dosage forms is also disclosed by the records of large quantity purchases by the Armed Services Medical Procurement Agency (now Military Medical Supply Agency). Thus between 1949 and 1956 the price per bottle of procaine penicillin (1,500,000 units in aqueous suspension) went down from $1.09 to 10.5 cents, as each manufacturer reduced the price in turn. Dihydrostreptomycin sulfate prices took a similar though less precipitous downward course, and in early 1956 were 14 percent of the 1949 price. Later in 1956 they recovered to 20 percent of the 1949 price. Prices paid by the Government for these drugs have been well below those paid by civilians.

The first broad spectrum antibiotic, American Cyanamid's Aureomycin (the generic name being chlortetracycline), was introduced at a price to retailers and hospitals of $15 for 16 capsules of 250 milligrams each on December 1, 1948. Two months later the price was reduced to $10. On March 25, 1949, Parke, Davis put Chloromycetin (chloramphenicol) on the market at the same price per capsule. On February 1, 1950, both companies reduced their prices to $8. Two months later, Chas. Pfizer & Co. introduced its Terramycin (oxytetracycline) at $8.40. On May 1, 1950, Aureomycin and Chloromycetin were reduced to $6, a price which Pfizer did not meet until November 1 of the same year. The next reduction, to $5.10, was initiated by Pfizer on September 27, 1951, and was met by both the others on October 1. This price remained unchanged thereafter.

The price of Aureomycin had thus decreased 66 percent from 1948 to 1951, a period during which procaine, penicillin and streptomycin prices decreased by about the same amount, or 69 percent. These latter prices kept on declining after 1951, whereas broad spectrum prices did not. This contrast was related, on the supply side of the market, to the difference in number of producers. There were 13 makers of procaine penicillin and 7 of the streptomycins in 1951 as against only 3 makers of the broad spectrum antibiotics.

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A fourth broad spectrum antibiotic, tetracycline, was added in 1953, at the same price as the others. Only one new producer was thus brought into the broad spectrum business, which in 1956 had 4 manufacturers (3 of them having exclusive products) plus 2 licensed sellers, as against 7 manufacturers making and 9 selling (2 of them out of stocks on hand) procaine penicillin and 5 making and selling the streptomycins. Price alternatives for some customers, and the possibility of additional price competition under certain conditions, are afforded by the non-manufacturing packagers of procaine penicillin and the streptomycins.

In 1951 Aureomycin accounted for 41.5 percent, Chloromycetin for 36.5 percent, and Terramycin for 22.0 percent of the dollar sales of broad spectrum antibiotics for medicinal purposes. In 1956 they accounted for 12.1, 15.7, and 20.6 percent of medicinal sales, respectively, while the new product, tetracycline, accounted for 51.6 percent.

By contrast with the stability of broad spectrum prices quoted to distributors, hospitals, and consumers after 1951, prices charged the Armed Services Medical Procurement Agency continued to decline. Between 1950 and 1956, for example, prices it paid for Terramycin dropped 62 percent as compared with the 39 percent decline (all of it prior to October 1951) in Terramycin prices quoted to retailers.

Records of the Veterans' Administration show it to have been purchasing tetracycline in 1954 at $24.22 (less 2 percent for cash) per bottle containing one hundred 250-milligram capsules—the same price paid by drug wholesalers then and later. In October 1954 Cyanamid offered to cut the price 10 percent, to $21.80 (less 2 percent), but Pfizer took the contract with a further 10.2-percent reduction, to $19.58 (less 2 percent). When purchasing on sealed bids was instituted in 1955, $19.58 less 2 percent, or precisely $19.1884, was bid several times by all manufacturers, except that Pfizer became low bidder on the two largest contracts by naming a net cash price of $19.188.

On one Veterans' Administration contract for 50,400 bottles (of capsules) in October 1956, to be delivered to 3 destinations, Pfizer reduced its bid another 10 percent, or to $17.63. Cyanamid was still bidding $19.58, though 2 weeks earlier it had sold 90,000 bottles (of tablets), to be delivered to the Armed Services Medical Procurement Agency at one destination, at an $11 price.

7. Analysis of financial data submitted by antibiotics manufacturers

In 1956 net sales of antibiotics from domestic production of Chas. Pfizer & Co. were equal to 39.4 percent of its consolidated net sales (which includes some production in plants abroad). The percentages

for the other 11 manufacturers ranged from 20.4 down to 4.6 percent. Thus antibiotics constitute merely a segment of the pharmaceutical industry.

American Cyanamid led the industry in dollar sales of antibiotics in both 1950 and 1956, its percentage of the total increasing from 23.1 to 26.6 percent. Pfizer was in second place, with 12.6 and 20.8 percent. Lilly advanced from sixth (7.7 percent) to third (9.5 percent). Olin Mathieson was fourth in both years (9.0 and 9.2 percent), while Parke, Davis dropped from third (10.4 percent) to fifth (7.3 percent).

The top 4 had 55.1 percent of sales in 1950 and 66.1 percent in 1956. This 11-point gain was slightly less than the combined gain, 11.7 points, of Cyanamid and Pfizer. Their great expansion resulted almost entirely from successful ventures in the broad spectrum field. Four of the 16 companies producing antibiotics in 1950 had dropped out before 1956.

These 16 companies responded at least in part to the Commission's cost questionnaire sent out in May 1957, though all companies stated that full cost data were not kept for individual antibiotic products or for the companies' antibiotics business as a whole. When the same plant was used for more than one product, manufacturing costs as submitted were based in part on allocations. Certain expenses of selling and administration were also allocated, usually on the basis of relative sales. The Commission has not had the accounting manpower available to verify these figures or allocations, but presents ratios based upon them at their face value. The fact that allocations are necessary makes it impossible to draw firm conclusions when the differences in ratios are small.

There have been considerable variations in the calculated ratios of profit before Federal taxes to net sales on antibiotics operations. The most profitable company in the 1950–56 period had the most stable ratio, ranging from a high of 53.7 to a low of 37.9 percent. For all other companies the spread between the high and low years was much wider. Seven reported net losses on antibiotics operations in one or more years.

In 1956, this ratio of net profit before taxes to sales ranged between 1.8 and 40.5 percent for the 9 companies submitting comparable data. Other ratios showed similar variations: cost of goods sold between 21.4 and 77.6 percent; advertising and selling expenses between 9.6 and 30.7 percent; research costs between 3.5 and 10.5 percent; and administrative and general expenses between 2.1 and 14.2 percent.

If 1956 figures for all reporting companies are averaged, 39.0 cents of each dollar of net sales of antibiotic substances represented cost of goods sold, as against 44.4 cents in 1950. Selling and advertising expenses came to 21.6 cents (12.9 in 1950), research to 6.7 cents (4.4

in 1950), and administrative and general to 8.7 cents (7.6 in 1950). After account is taken of 3.2 cents of income from royalties and licenses and 1.2 cents in other costs, 26.0 cents remained in 1956 for net profit before Federal taxes. Reported net profit had been as low as 19.3 cents per dollar of sales in 1952 and as high as 34.5 cents in 1951.

For 1950, the company responses showed penicillin, the broad spectrum antibiotics, the streptomycins, and "all others" (consisting almost entirely of combinations, and bacitracin) accounting for 44.4, 35.4, 13.4, and 6.8 percent, respectively, of total dollar sales of antibiotics exclusive of one specialty penicillin. In 1951 the broad spectrum group took over first place, and in 1955 it accounted for 56.1 percent of the total. In 1956 it accounted for 50.9 percent, and all penicillin, the streptomycins and "all others" (more than half of which now consisted of combinations and erythromycin) for 19.0, 3.9, and 26.2 percent, respectively.

The 1956 ratios of net operating profit to net sales were as follows: recently patented and higher priced penicillins, 43.4 percent; broad spectrum group, 36.8 percent; "all others," 17.2 percent; older penicillins, a deficit of 5.6 percent; streptomycins, a deficit of 41.4 percent. In 1950 and 1951, just prior to the severe competitive price cutting of 1952, penicillin and the streptomycins had shown net operating profits equal to about 20 percent of net sales.

The streptomycin figures (which are missing for 1 of the 3 largest producers since it did not furnish a usable breakdown) indicate successive deficits of 4.7, 20.9, 37.4, and 41.4 cents per dollar of sales from 1953 through 1956, while physical output was rising to a new peak. If such losses occurred, it is easy to see why one firm ceased production in 1955 and another in 1956. Other companies have stated that they stayed in business for such reasons as reluctance to drop a needed product from their line, or hope of increased world demand.

Regardless of the exactness of particular allocations, it is clear that the recently patented penicillins, the broad spectrum antibiotics, and some at least of the antibiotic combinations and specialties in the "all others" group have yielded higher profits than the older, nonexclusive penicillins and streptomycins.

Six companies submitted usable data from which net profit before Federal taxes on antibiotics could be computed as a percentage of assets devoted to antibiotics operations. Such profit ratios ranged in 1956 from 2.0 to 57.6 percent, and in 1950–55 from deficits for 3 companies in at least one year to a profit of 101.2 percent for one company in 1950. The weighted average returns for the seven successive years were 42.2, 37.1, 18.2, 19.4, 20.6, 23.3, and 28.5 percent.

Ratios of profits to assets on antibiotic operations for 5 of these companies were compared for 1950–56 with (1) ratios of total phar-

maceutical profits to pharmaceutical assets of the 5 companies; (2) profit ratios of 10 pharmaceutical companies not making antibiotics; and (3) profit ratios on the consolidated operations of the 10 antibiotics manufacturers which publish financial statements. The first comparison showed higher average antibiotics profits for 1950–55, but higher pharmaceutical profits for 1956. The second showed a lower average profit ratio for the 10 nonantibiotics companies than for the antibiotics companies in 1950 and 1951, but a higher ratio from 1952 to 1956. The third brought out that the nonpharmaceutical profit ratios of the antibiotics companies were significantly lower throughout than their profit ratios either on antibiotics or on all pharmaceutical operations.

Profit comparisons on the basis of sales were made for six antibiotics companies which furnished data on both their antibiotics and pharmaceutical operations. (1) Two companies showed higher antibiotics than pharmaceutical profit ratios each year, 2 others in 3 of the 7 years, and the 2 remaining companies in none of the years. (2) The 10 nonantibiotics companies showed higher profit ratios in 5 of the 7 years and approximately the same ratios in the other 2 years. (3) Nonpharmaceutical operations of the antibiotics companies were, as in the asset comparison also, less profitable than pharmaceutical operations.

This ratio of profits before Federal taxes to assets employed in antibiotic operations, for the six companies submitting usable data, was higher each year from 1950 through 1956, than the same ratio for chemical manufacturing, and still higher than for all manufacturing. The antibiotics ratio was slightly higher than that for "Drugs and Medicines," in the only year 1956, for which the latter series was available.

The Commission recognizes that relative profit ratios depend on basic factors such as trends in demand costs, efficiency, and technology, as well as on risks and the degree of competition. It has not made an assessment of antibiotics profits in the light of these factors.

8. Patent ownership and licensing in the antibiotics industry

The penicillin discoveries of Drs. Fleming, Chain, and Florey were not patented. Patents on the basic process improvements developed by scientists of the United States Department of Agriculture were licensed freely in accordance with United States Government policy. From these discoveries and the likewise unpatented improvements in the penicillin mold in 1943, a new branch of the pharmaceutical industry came into being.

Patent Office classification files, supplemented by data submitted by 11 manufacturers in response to the first FTC data request, disclose that 671 antibiotics patents had been issued through September 1956.

Of these, 576 were assigned to domestic corporations. The remaining 95 went to foreign corporations, individuals, the United States Government, and miscellaneous patentees such as research foundations. The antibiotics companies have often emphasized the importance of obtaining product patents on new drug discoveries.

The first significant product of company-financed research was streptomycin, discovered in 1943, marketed in 1946, and patented in 1948. The next important products of research were dihydrostreptomycin and procaine penicillin. Both of these were discovered in the mid-1940's, marketed in 1948, and patented in 1950.

Streptomycin, first announced in January 1944, was the discovery of Dr. Selman A. Waksman and his assistants at Rutgers University, working on a grant from Merck & Co. Merck, upon request, gave up its contractual "sole right to develop commercially" any results of this research. The Rutgers Research and Endowment Foundation became the patent assignee and licensed eight producers—all of which had undertaken construction of streptomycin plants in 1945.

Research on streptomycin revealed that a further hydrogenation process would produce dihydrostreptomycin, which was considered superior to streptomycin for certain purposes and valuable in combination with it for certain others, and which quickly took over the bulk of the sales. Three companies having claimed priority, a Patent Office interference proceeding was declared. This was dissolved when Parke, Davis and E. R. Squibb conceded priority to Merck. Merck licensed the companies producing streptomycin to make this easily derived but essential improvement, dihydrostreptomycin.

Severe price competition grew out of this ease of entry into production of "the streptomycins," and by 1950 streptomycin itself was being spoken of as "distress merchandise." On the one hand, purchasers benefited; on the other, the number of producers dropped to five by 1956.

Beginning in 1944 and 1945, several experimenters discovered that mixing penicillin with procaine (hitherto used as an anesthetic) yielded an antibiotic substance which would stay in the blood stream much longer than any then available form of penicillin. After a Patent Office interference involving five companies, Eli Lilly received the basic product patent on the procaine penicillin salt in July 1950. Fourteen companies, including Lilly, had been manufacturing this substance since 1948. Ten of these, and one not manufacturing in 1948, negotiated licenses with Lilly, 8 on a royalty basis and 3 royalty free because of what Lilly deemed reciprocal advantages. Lilly filed infringement suits against three other companies which refused to pay royalties, and secured settlements in 1953, 1954, and 1956, respectively. These 3 are among the 5 companies which have dropped out of the

procaine penicillin business. By 1956, partly as a consequence of sharp price competition, the number of manufacturers of procaine penicillin had decreased to 7, although 2 others continued to sell out of stocks on hand. Between October 1950 and September 1956, 16 more patents on methods of preparation and compositions of procaine penicillin were issued to 8 applicants.

Later developments, including public statements by company officers, made it plain that the antibiotics research programs instituted by the companies during and shortly after World War II did not have as their aim the discovery of drugs for which the patents would be licensed as widely as were, in fact, the three just reviewed. Each company was seeking exclusive products which would support profitable prices and thus yield wider profit margins than those which price cutting was to produce on these three.

Some of the most important patents that subsequently issued as a result of these research programs, the companies whose scientists received each patent, and the dates of issuance (which were usually later than the date of first commercial production), were:

Chlortetracycline	American Cyanamid	1949
Chloramphenicol	Parke, Davis	1949
Oxytetracycline	Pfizer	1950
Phenoxymethyl penicillin (penicillin V)	Lilly	1951
Benzathine penicillin	American Home Products	1953
Erythromycin	Lilly	1953
Tetracycline	Pfizer	1955

Lilly is also American licensee under an improvement patent on phenoxymethyl pencillin held by an Austrian firm.

The prices on these products have been considerably higher, when translated into per-gram equivalents, than those prevailing at the same time on the streptomycins and older forms of penicillin. The patentees either licensed no one or licensed not more than three other manufacturers, and the kind of price cutting that marked the earlier products has not, under these circumstances, developed.

The licenses actually granted on these newer patented products were in most instances the result of settling either Patent Office interference proceedings or infringement suits, or of prior agreements among companies doing research in the same field. The patentee of each of the first three broad spectrum antibiotics has retained the exclusive right to manufacture it for sale. Phenoxymethyl penicillin is licensed by Lilly to Wyeth Laboratories (American Home Products Corporation). American Home Products has licensed Bristol, Lilly, and Pfizer, which had been its opponents in interference proceedings, under the benzathine penicillin patent. Erythromycin was licensed to Abbott Laboratories and The Upjohn Co., possibly as a result of a cross-licensing agreement dating from the penicillin research program of World War

II and extended by the parties in 1948 to all patent applications filed before July 18, 1957, provided they related to antibiotic cultures known by July 18, 1952. Finally, tetracycline was licensed to American Cyanamid and Bristol to make, use, and sell, and to Olin Mathieson and Upjohn to package and sell, through agreements settling interference proceedings and infringement litigation.

Eleven major manufacturers were involved in 70 interference proceedings arising out of applications leading to issuance of patents through September 1956. One reason for such interferences is the nature of research in this industry (and, it is known, in many others), whereby several companies may pursue the same lines of inquiry simultaneously. Fifty interferences were settled by agreement—35 in penicillin, 6 in the streptomycins, 1 in tetracycline, and 8 in other products. The companies either agreed not to contest the decision of the Patent Office as to priority and invention, or settled the issue of priority among themselves and withdrew all the patent applications but one—with the prospective patentee pledged to license the other applicants at a stipulated royalty.

Two examples of patent litigation in the industry are reviewed in highly condensed fashion in the report. One, involving the application in 1945 by the late Dr. Simon L. Ruskin for a basic product patent on the salt of procaine pencillin, illustrates the difficulties faced by an independent inventor in this field.[3] In 1949 the Patent Office declared an interference among Bristol, Lilly, Merck, Pfizer, and Dr. Ruskin. By 1950 Bristol, Merck, and Pfizer had conceded priority to Lilly, which received the basic product patent. Dr. Ruskin prosecuted his own application before the Patent Office against opposition by Lilly. In 1954 he received a patent on "procaine penicillin preparation," containing the claim "procaine salt of penicillin." On the same day, he filed infringement and damage suits against Lilly, and Lilly sued to have his patent declared invalid. In 1957, 12 years after Dr. Ruskin had first applied for his patent, he sold it to Union Carbide Corp., which at once settled the lawsuits with Lilly.

The tetracycline litigation grew out of the claimed discovery of this antibiotic at about the same time by scientists working in the laboratories of four companies. Two interferences were declared at the Patent Office. The first, between American Cyanamid and Pfizer, was terminated in February 1954 when Cyanamid conceded priority in conjunction with a cross-licensing agreement. The second involved Cyanamid, Bristol, and Pfizer—Cyanamid as a result of its purchase of the antibiotics division of Heyden Chemical Corp., which had pending a patent application on a chemical salt of tetracycline.

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[3] The Commission expresses no opinion in this study of the merits of this or any patent claims.

In October 1954 this "salt" interference was dissolved by the patent examiner on the ground that the Heyden application had disclosed that tetracycline had been in fact produced before the alleged dates of invention as a byproduct of the manufacture of Cyanamid's chlortetracycline. On December 6, 1954, and February 25, 1955, Cyanamid and Bristol formally abandoned their claims. Pfizer had pushed its application, and received the patent on January 11, 1955.

Bristol had been manufacturing tetracycline since April 1954, and selling in bulk to Squibb (Olin Mathieson) and Upjohn for resale under their own labels. Immediately on receiving the product patent, Pfizer sued the three companies for infringement. They filed declaratory judgment actions in another jurisdiction claiming that the tetracycline patent was invalid both for the reason originally given by the examiner and because it had been allegedly obtained through misrepresentation.

In March 1956 the lawsuits were settled out of court. Bristol recognized Pfizer's patent, agreed to pay royalties, and licensed Pfizer, at its option, to use and pay royalties on a process patent which Bristol had received for direct fermentation of tetracycline. When Cyanamid had recognized the priority of Pfizer's claim in January 1954, it had agreed to pay royalties on all tetracycline it manufactured if Pfizer should obtain a patent, while Pfizer had agreed to pay royalties to Cyanamid on the chlortetracycline it necessarily manufactured and used (not sold) in the making of tetracycline. A third link in the final settlement had been forged in January 1955 when an infringement suit by Cyanamid against Bristol for manufacturing chlortetracycline in the process of making tetracycline had been withdrawn upon Bristol's agreement to pay Cyanamid (as it was later to agree to pay Pfizer) a royalty on all its sales of tetracycline. Finally, Pfizer's suits against Olin Mathieson and Upjohn and the actions of these companies against Pfizer were settled by Pfizer's granting them licenses to continue repackaging and selling tetracycline purchased in bulk from Bristol.

The conclusion of the whole proceedings was that the manufacture of tetracycline was restricted to the 3 companies which had made patent applications on the product, and its sale to these and 2 others. In 1956 American Cyanamid accounted for 55 percent of the volume of output.

9. Trademarks and fair trade in the antibiotics industry

Trademarks and trade names are used extensively to designate the antibiotic products marketed by particular companies, and thus to establish lasting preferences in the minds of physicians and purchasers. Tetracycline, for example, is quoted and sold in the ethical drug

markets as Achromycin, Tetracyn, Polycycline, Steclin, and Panmycin (by American Cyanamid, Pfizer, Bristol, Olin Mathieson, and Upjohn, respectively). ABBOTT, BRISTOL, and UPJOHN are examples of trade names, designating products of these companies.

Large manufacturers generally sell their penicillin dosage forms at higher prices than do the smaller packagers, although frequent exceptions were noted in chapter VI. Evidently the trademarks and trade names of the former usually have a greater attraction for physicians, pharmacists and hospitals than do those of the latter.

In 1954 at least 550 trademarks and trade names were used by various sellers to designate over 100 different antibiotic preparations, and by 1956 there were 60 additional names for combinations alone. The multiplicity of names has created confusion for doctors, and it led to criticism by the Journal of the American Medical Association as early as 1946. Even a nonspecialty product like procaine penicillin in aqueous suspension, which was marketed in 1956 by at least 22 companies was sold by 9 of these (7 being major manufacturers) under trademarks consisting of prefixes, some of them abbreviating the firm's own name, followed by "cillin." At least 13 other companies (only 2 being major manufacturers) sold this item under its generic name.

Whatever the difficulty caused for users by the multiplicity of such names, both trademarks and trade names can serve useful functions. Trade names of manufacturers are required to be placed on all antibiotics sold in commerce. Trademarks may afford manageable short names for combinations of certain antibiotics and other drugs, especially when the latter have almost unpronounceable generic names. Trademarks are especially important in doing business in those countries which deny patent protection on medicines.

Several of the antibiotics manufacturers have established minimum resale or "fair trade" prices for many of their trademarked products, under the provisions of State fair trade laws and Federal implementing legislation. The percentage markup on cost which these prices, so far as they are effective, protect for the retailer is generally 50 percent. This means that the retailer's margin—if he purchases at the manufacturer's quoted price to retailers and sells at the fair trade price—is a third of the price paid by the consumer.

10. Antibiotics and the public

In the 1940's antibiotics quickly won an important place in the ethical drug market of the United States. In 1950 manufacturers' sales minus exports, for all grades including animal feed supplements, was a little less than 1 gram (0.0020 pound) per capita, of which 96 percent consisted of the medicinal grades. Sales minus exports in 1956 were nearly 4 grams (0.0085 pound) per capita, 72 percent being

medicinal grade. These figures are an approximation of total domestic consumption, disregarding inventory changes, but consumption would in fact be a little lower after correction for spoilage through loss of potency.

It has been estimated that consumer spending for all grades of antibiotics amounted to $575 million in 1953—a year in which the major manufacturers' sales from their own production came to $244 million. The difference (so far as it is not due to errors of estimate) is in the cost of the services of finishing and packaging by others than original manufacturers, and in the overall cost of distribution.

The most widely used antibiotic is procaine penicillin. The retail list prices advertised to the trade for vials containing 10 injections of 300,000 units each, at the end of 1956, ranged from 94 cents to $1.73. It is impossible to deduce from retail prices of 9.4 to 17 cents per injection the actual cost to the patient, since it is the charge of the hospital or the physician rather than the price of the drug which determines the amount he pays. This qualification does not apply in the case of prescriptions taken orally, since here the patient pays the cost of the drug directly. For example, the published retail list price for sixteen 250-milligram capsules of the broad spectrum antibiotics is $8.50, or 53 cents per capsule, and the fair trade price is $7.65, or 48 cents per capsule. Any physician's fee is additional.

Antibiotics represented an estimated 1.5 percent of all prescriptions written in 1948, and 12.7 percent in 1955. In 1952 and in every year since, more prescriptions have specified antibiotics than any of the other seven categories of ethical drugs. More than 50 new "antibiotics—sulfa and combinations" prescription specialties have been introduced annually.

Antibiotics have made their contribution to public health both in treating infections and contagious diseases of bacterial origin and in preventing complications that may follow illnesses (such as colds, influenza, measles, and other viral infections) which themselves are unresponsive to antibiotics therapy. Each antibiotic which is of value shows capacity to inhibit the growth of or kill particular disease-causing micro-organisms, and the overlapping of these capacities makes antibiotics substitutable for each other in many instances. But there are certain infections for which a given antibiotic is considered the "drug of choice."

The importance of antibiotics among the factors at work in reducing disease and death rates is illustrated by the declining number of reported cases in the United States of the group of illnesses whose bacteria can be controlled by their use. There were approximately 1.2 million such cases in both 1946 and 1947, 1.0 million in 1948, and beginning in 1951, less than 800,000 in each year. Antibiotics have un-

questionably contributed to sharp reductions in the death rates from such important causes of death as tuberculosis and venereal diseases.

Antibiotics have proved particularly effective in saving the lives of children and young persons. The sheer economic value of these lives, measured by future productiveness, may be considered substantial.

A decline of several days in the average time spent by patients in hospitals is due in part to the use of antibiotics, although also to other factors such as changed medical practice.

The discussion in this report has been confined to the effects of antibiotic drugs on health in the United States. It does not cover the effects of this American industry on health in foreign countries.

General Summary

This report traces the development of an industry which did not exist in 1941 but whose net sales reached $344 million 10 years later, whose output then doubled from 1951 to 1956, although lower prices for some products and in new markets kept dollar sales below the 1951 peak. Its history has been one of expansion at home and abroad to meet rapidly increasing demand, and of heavy reliance on laboratory research for new products and product improvements. Yet the manufacture of antibiotics is not, in fact, a separate industry. It is part of the ethical drug segment of the pharmaceutical industry. Sales of antibiotics from domestic production were about 40 percent of the consolidated 1956 sales of one manufacturer, but 20 percent or less for the 11 others.

Penicillin was discovered in England, in 1928, and its capacity to attack disease-causing micro-organisms was proved in 1939–41. The industry was established during World War II, when the United States Government undertook to obtain penicillin for the Armed Forces. Commercial and nonprofit research were marshalled, the problems of large-scale production were solved, 20 pharmaceutical companies undertook manufacture, and plant construction was speeded through public and private investment. In 1945 this unique experiment in Government promotion of a new medicine gave way to further development by private enterprise.

Sodium and potassium penicillin, the chief types produced in the first years, were not patented. By early 1948 three important new antibiotic substances had emerged from company laboratories or from research paid for by industry and quickly became volume leaders. Rutgers University held the patent on streptomycin and gave licenses to eight companies that made application. Merck & Co., which had subsidized the Rutgers research, later received a patent on the closely related dihydrostreptomycin (whose sales grew as those of strepto-

mycin declined), and it licensed the same companies. Eli Lilly & Co., which obtained the patent on procaine penicillin in 1950, then or later licensed 14 companies, 13 of which had begun its manufacture in 1948.

Notable increases in output and reductions in cost resulted from improvement of antibiotic culture strains, facilities, and processes, and from expansion and modernization of existing capacity as part of the Korean war program. Between 1948 and 1956 the output of penicillin increased by 6 times and that of the streptomycins by almost 8 times, and the production of antibiotics introduced after the late 1948 reached 45 percent of the 1956 total. The additional output, the advent of new antibiotics which could be taken orally, and above all the spectacular cost reductions, set the stage for price reductions. Through competition of the numerous makers of penicillin and the streptomycins, bulk prices of these products were forced down by more than 99 percent from their introductory levels. Only 7 companies were still making procaine penicillin in 1956, and 5 were still making the streptomycins.

The individual producers concentrated their post-World War II research efforts on the discovery of patentable antibiotics, which could be marketed as exclusive products possibly insulated against aggressive price competition. At most, they were willing to grant licenses to those competitors whose parallel research had made them rival applicants for patents covering the same product, or in some instances to partners in research pooling and patent exchange agreements. During the period 1949–56, 29 new antibiotic products were developed, of which 21 were still being produced in 1956.

Three "broad spectrum" antibiotics, which attacked a wide range if micro-organisms, appeared in 1948, 1949, and 1950. They competed in use, and at first (to some degree) in price, with antibiotic substances already on the market. Thus the price of the new Aureomycin decreased by 66 percent from December 1948 to October 1, 1951, while prices of the older penicillins and streptomycins were decreasing by 69 percent. Since 1951, published quotations of the broad spectrum products have remained unchanged, and all important antibiotics more recently introduced have been offered at about the same price level, while prices of the earlier products continued down.

By 1956 published prices of major manufacturers for one popular injection form of procaine penicillin were the equivalent of 19 cents per gram (a 94-percent reduction from the introductory price in 1948). A dosage form of potassium penicillin tablets (less often used than the injection form, but more comparable to broad spectrum tablets in their finishing and packaging processes) was offered at the equivalent of 76 cents a gram by 5 major manufacturers and 27 to 44 cents a gram by "packagers"—whose names commanded less recognition

among buyers and which bought their penicillin in bulk from the manufacturers. In contrast, the per-gram price equivalents of various dosage forms of the broad spectrum antibiotics, of erythromycin and of the patented benzathine and phenoxymethyl (penicillin V) penicillins ranged from $1.12 to $1.51.

The effects on profits of this price difference between the older and newer antibiotics are indicated by certain financial data submitted by the companies and tabulated under several major product categories. As late as 1951, net operating profit reported was 23 percent of sales for the older forms of penicillin, 21 percent for streptomycin, and 50 percent for the broad spectrum group. A deficit was shown every year from 1952 through 1956 for the older penicillins, and from 1953 through 1956 for the streptomycins. Broad spectrum net operating profits, despite rising costs of, and increasing expenditures for, selling, research and management, were reported to be 37 percent of sales in 1956, and profits on the new, exclusive penicillin products to be 42 percent. As a result of allocations of joint costs, the specific figures are subject to a margin of error, but the broad divergence in profit trends emerges clearly.

In 1950 the combined sales of American Cyanamid Company and Chas. Pfizer & Co. were 35.7 percent of all antibiotic sales. By 1956 the share of these companies, both of which had developed successful new antibiotics, had increased to 47.4 percent. Some companies less fortunate in their research have at times suffered losses, and four of the 1950 producers have discontinued manufacture. Nevertheless, the production of antibiotics, like that of drugs and medicines generally, has been among the most profitable branches of manufacturing in recent years. The Commission has not attempted to assess these profits in the light of industry risks or other factors. The continuing emergence of new antibiotic drugs does, however, make it appear that (in the words of the Commission resolution which initiated this study) profits have been adequate to give the desired "continuing incentives for the discovery and development of new uses and new antibiotics under the private enterprise system."

One significant aspect of competitive rivalry in the antibiotics industry is the attempt by manufacturers to hold and increase their shares in the ethical drug market by product improvement, by product identification through trademarks, and by heavy promotional expenditures. A characteristic of the whole pharmaceutical industry is that selling costs represent a substantial part of the manufacturer's price. Costs and profits of distributors, such as wholesalers, retailers, or hospitals, must be added to arrive at the price paid by the physician or patient. This distributive margin appears to range from perhaps

a third to a little over half of the price. Due to limitations of funds and personnel, the Commission's study did not cover this area in detail.

The importance of antibiotics in medicine is revealed by public health statistics showing the declining incidence of, and death rate from, illnesses such as tuberculosis and the venereal diseases, in the treatment of which antibiotic therapy has proved effective. More antibiotic prescriptions than any other type have been written by physicians since 1952. Antibiotic substances have also found important secondary uses, especially as animal feed supplements. Finally, the American industry has supplied, through exports and plant construction abroad, much of the world demand for these drugs.

In its economic survey of the industry, the Commission has taken note of any situations which might represent a conflict with the laws it enforces. Thus, certain patents have been handled in ways that may represent a conflict with the antitrust laws, instances of uniformity of bids and unusual rigidity of prices were observed, and the provisions of some term purchase contracts appeared to warrant further study with respect to differences in prices charged different buyers and to relationships established between the parties. All situations having a possible trade restraint aspect have been made the subject of a legal investigation by the Commission since November 1957.

CHAPTER I

Origin of the Industry

This chapter presents information as to the discovery of penicillin, the first medically useful antibiotic, and describes developments which led to large-scale commercial production of penicillin during World War II. Some significant features are not dealt with in this chapter, but are considered in detail in appendix II to the report.[1]

Science—The Endless Frontier,[2] a report to the President on a program for postwar scientific research by Dr. Vannevar Bush, Director of the Office of Scientific Research and Development, opens its first chapter with this paragraph:

> We all know how much the new drug, penicillin, has meant to our grievously wounded men on the grim battlefronts of this war—the countless lives it has saved—the incalculable suffering which its use has prevented. Science and the great practical genius of this nation made this achievement possible.[3]

In the next chapter the achievement is explained:

> Penicillin reached our troops in time to save countless lives because the Government coordinated and supported the program of research and development on the drug. The development moved from the early laboratory stage to large scale production and use in a fraction of the time it would have taken without such leadership.[4]

Fleming's Discovery

One of the more concise summaries of the origin of penicillin and the manner of its reaching the United States is found in the 1943 report of the Bureau of Agricultural and Industrial Chemistry, United States Department of Agriculture:

> Penicillin was discovered in 1929 [but see Fleming quotation below] [5] by a British bacteriologist, Prof. Alexander Fleming, who observed a germ-free zone surrounding a small particle of mold which contaminated an agar-plate culture of a staphylococcus species. The mold was identified as *Penicillium notatum* and consequently the germ-inhibiting substance excreted by the mold was named

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[1] App. II presents in detail the data summarized in this chapter and additional information that could not be treated in this summary. Included is a recital of the unsuccessful efforts made during World War II to achieve the commercial synthesis of penicillin.

[2] Vannevar Bush, Science—The Endless Frontier, U. S. Government Printing Office, Washington, 1945.

[3] Ibid., p. 5.

[4] Ibid., p. 9.

[5] "The contamination in 1928 of a culture plate by spores of a species of *Penicillium* was the beginning of the study of penicillin. Such contamination is not uncommon in a

"penicillin." Further investigation was stimulated by the war. In 1940 other British investigators, led by Prof. H. W. Florey and Dr. E. Chain of the University at Oxford, succeeded in preparing a small quantity of the drug in concentrated form, which was administered to human patients for the first time in 1941, with marked success.

Professor Florey was so impressed with the possibilities of this drug for treating gangrenous wounds and infected burns that he and an associate, Dr. N. G. Heatley, came to the United States to urge that attempts be made to produce the drug commercially. He was encouraged by the Chemotherapy Committee of the National Research Council and the Committee on Medical Research of the Office of Scientific Research and Development of the Office for Emergency Management which arranged to support concentrated research for a limited time on penicillin production at the Northern Regional Research Laboratory by its Division of Fermentation Research, in cooperation with Dr. Heatley and four other scientists, representing the Office of Scientific Research and Development.[6]

As noted in the above quotation, responsibility for the work of coordinating penicillin research was entrusted to the Committee on Medical Research of the Office of Scientific Research and Development. The Committee was organized in June 1941, to "initiate and support scientific research on medical problems affecting the national defense," and from the beginning availed itself of the experience and advice of the already functioning committees of the National Research Council. Its chairman throughout its history was Dr. A. N. Richards.

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bacteriological laboratory and is usually regarded as a reflection on the technique of the bacteriologist. Sometimes, however, it is unavoidable, as in this particular instance when the culture plate had to be opened for examination under a dissecting microscope and then left for future examination. When next observed, mould spores which had gained access had developed into a large colony. This in itself did not call for comment, but what was very surprising was that the staphylocooccal colonies in the neighborhood of the mould, which had been well developed, were observed now to be showing signs of dissolution. This was an extraordinary and unexpected appearance and seemed to demand investigation. The mould was therefore isolated in pure culture for further examination. It was found to belong to the genus *Penicillium*, but it was not so easy to identify the species. There are some hundreds of species of *Penicillium* and the mycologist attached to St. Mary's Hospital classed it as *P. rubrum,* and in the first publication on penicillin this name appeared. Later work, however, by Raistrick and Thom showed that it really was *P. notatum,* a species closely allied to *P. chrysogenum* (Thom). * * *

"In 1929 the position was that a mould—a *Penicillium*—produced in culture a remarkable antibacterial substance (penicillin). This acted on many of the common bacteria pathogenic to man. The strength of a broth culture of this mould was such that it could be diluted to nearly 1 in 1,000 before it lost its bacteriostatic power against staphylococci. This is about three times the dilution at which phenol ceases to be bacteriostatic. In contrast to all the older antiseptics it was apparently without toxicity to human leucocytes, but it was unstable and easily destroyed. The earliest attempts at concentration failed, but the crude fluid continued to be used for selective culture in the bacteriological laboratory." (Sir Alexander Fleming, "History and Development of Penicillin," Penicillin, Its Practical Application, edited by Sir Alexander Fleming, 2d ed., Butterworth & Co., Ltd., London, 1950, pp. 2–4, 11.)

[6] Report of W. W. Skinner, Chief of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agricultural Research, dated October 15, 1943.

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According to the Medical Advisory Committee appointed by Dr. Bush, "among the most conspicuous achievements" of the Committee on Medical Research was—

The acquisition, in civilian hospitals and laboratories of sufficient knowledge of the therapeutic value of penicillin to warrant its official adoption by the medical divisions of the Army and Navy, and to provide the impetus for the great production program that has made this remarkable drug available in large quantities for both military and civilian use.[7]

First Efforts of OSRD To Obtain Production of Penicillin

Once the Committee on Medical Research was convinced of the potentiality of penicillin as a military medicine, its efforts were immediately directed toward problems of production as well as toward problems connected with therapy.[8] It was hoped that penicillin could be manufactured by chemical synthesis, avoiding the tedious mold-growth process by which only samples of penicillin had so far been obtained.

In his testimony on October 22, 1945, at the Senate hearings on science legislation, Dr. Richard told of Dr. Bush's having "called a meeting in his office in October of * * * [1941], at which scientific representatives of four industrial firms were present, also the chief mycologist of the Department of Agriculture, the Chairman of the Division of Chemistry of the National Research Council, the Chairman of CMR [Committee on Medical Research] and Dr. Bush himself, in order to find out whether a joint effort might not be initiated which would give us more information as to the possibility of producing that drug here."

"It was all a gamble," said Richards. "The representative of one particular firm was enthusiastic about cooperation. The others didn't know too much about it and were cautious."

Continuing his account of the early attempts to obtain the cooperation of the companies in question, Dr. Richards said:

Another conference was held in December of the same year, at which the heads of companies were present, and it was agreed that information would be shared through the intermediation of the Committee on Medical Research, and all four companies agreeing to put their research teams or fractions of them on the problem. As a result, we began to get a trickle of a supply of penicillin during the early months of 1942.

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[7] Vannevar Bush, Science—The Endless Frontier, App. 2, "Report of the Medical Advisory Committee, Dr. W. W. Palmer, Chairman," p. 47.

[8] John Winslow Hirshfeld, "The Application of Penicillin to Surgical Problems," Advances in Military Medicine, edited by E. C. Andrus, *et al.*, 2 vols., Little Brown & Co., Boston, 1948, vol. I, p. 123.

We didn't have contracts with the commercial firms. They preferred not to work under contract and we got all the advantages of a contract without cost to the Government.

* * * * * * *

The production research by commercial firms was done at their own expense; OSRD, on recommendation by our committee, helped finance the work of the Peoria laboratory of the Department of Agriculture and, after February 1, 1943, bought all of the penicillin supplied to the clinical investigators.[9]

Dealing at a later date and in somewhat more detail with the earlier efforts (including the two meetings of which the Subcommittee was told) of the OSRD to stimulate the production of penicillin, Dr. Richards wrote:

From these meetings, all the participants received assurance of the interest of OSRD [CMR] and of the support that the OSRD was prepared to supply to their efforts. It was specifically agreed that the Peoria laboratory would energetically continue its study of the cultural characteristics of the mold, with a view to increasing its productiveness; that the Chief of the Fermentation Division would advise the cooperating companies of progress made and act as their consultant; and that, while the companies would proceed with production research independently, their progress would be reported to the CMR for such distribution as would advance the program.

Early in 1942 the OSRD made funds available to the Northern Laboratory[10] for extensive expansion of its work. The industrial companies chose not to apply for Government funds; indeed, for more than a year after these meetings the only penicillin that the CMR distributed for clinical studies was provided by three of these companies without cost to the Government. Priorities for the apparatus and equipment necessary for production research by the industrial firms were obtained from the War Production Board through the advice of CMR.[11]

Since Dr. Richards did not elaborate to the Senate subcommittee upon the statement that the commercial companies "preferred not to work under contract," or suggest in his foreword to Advances in Military Medicine why it may have been that "the industrial companies chose not to apply for Government funds," it should be understood that the OSRD did not solicit uncompensated services or fail to offer financial as well as other kinds of support. An OSRD record of the meeting of October 1941, mentioned in Dr. Richards' testimony quoted above, contains two paragraphs which at least make clear that preference and choice were involved in nonacceptance by "the industrial companies" of Government funds, and, may contribute towards an enlarged understanding of the companies' attitudes. The two relevant paragraphs of the memorandum are these:

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[9] Hearings before a subcommittee of the Committee on Military Affairs, U. S. Senate, 79th Cong., 1st sess., on S. 1297 and related bills, pt. 3, pp. 461–462.

[10] Northern Regional Research Laboratory, U. S. Department of Agriculture at Peoria, Ill.

[11] A. N. Richards, foreword to Advances in Military Medicine, edited by E. C. Andrus *et al.*, 2 vols., Little, Brown & Co., Boston, 1948, vol. I, p. li.

Various questions were asked and answered concerning priorities and concerning patents. The patent sheets of both the NDRC and CMR contract forms were supplied to each. Dr. Bush left two questions with them: (1) what each plans to do or is willing to do in this field, (2) how far they are willing to go in collaboration. It was made clear that the Government had money to spend and they are to think of how the Government can help them. The specific question was raised that if any one or all of the companies made sufficient product for both clinical and chemical testing, would they be willing to place enough for chemical study in the hands of certain university chemists.

The party broke up with the thought that they will consult with the responsible heads of their companies, and will let me know the answers to these questions or any others that have occurred to them with the thought that a further conference may be called. Dr. Bush emphasized the fact that we were not suggesting any commercial collusion at all; that we were only interested in the research aspects of the whole problem.[12]

By the latter part of April 1943, despite the impressive clinical evidence of the therapeutic value of penicillin, discouragement seems to have prevailed in the Committee on Medical Research—or at any rate on the part of its chairman—about the availability of much more adequate supplies of penicillin by any reasonably predictable date. In an effort to increase the available supplies, on April 27, 1943, Dr. Bush sought the help of Elihu Root, Jr., first talking to him on the telephone and then writing the letter quoted in part below:

* * * * * * *

One of the greatest medical discoveries of recent times, and probably the greatest medical matter to come out of the war, is penicillin. This is a product obtained from a mold. It is exceedingly potent * * * it has definite arresting action in dilutions as great as one part in a hundred million. It can be directly injected into the blood stream. Moreover, it acts especially on those cases that are resistant to the sulfa drugs, or that are caused by organisms on which the sulfa drugs fail to act. However, it seems to be more than just a supplement to the sulfa drugs and if it were available in sufficient quantity and at low enough cost it might well supplant them for many purposes.

The fact that such a potent substance existed has been known for quite a few years through observations in Great Britain. The problem has been to get enough of it to allow clinical tests to be made, and the problem following this is to get the cost down to where it can be used practically. Dr. Richards' committee has had a large amount of work going on both in university laboratories and with some of the pharmaceutical concerns. When enough of the drug was obtained for clinical testing, the results were quite remarkable. The cost has been brought down steadily. At present there is enough of the stuff so that really extensive treatments can be undertaken, and some very hopeful tests have come out of the Brigham Young Hospital in Utah on cases brought from Guadalcanal which had refused to yield to any other treatment.

Now the pharmaceutical companies have cooperated in this affair after a fashion. They have not made their experimental results and their development of manufacturing processes generally available, however. The Committee on Medical Research has brought about interchange as far as it could, but not

[12] Memorandum, Conference on Penicillin, October 8, 1941, records of OSRD, National Archives, Record Group (hereafter abbreviated NA, RG) 227.

complete interchange. Undoubtedly there could be expedition if the interchange were complete.

The problem is now well past its first experimental stages. There is no doubt whatever that the product is of enormous value. There is no doubt that it will need to be manufactured in very large quantities indeed. Now facilities will have to be built for such manufacture. The benefit that can come to our wounded is very great, and the results after the war may be a very large boon to humanity generally. However, WPB is faced with the problems of where and to what extent priorities should be extended for allowing new people to get into the manufacture, and the Committee on Medical Research is faced with the problem of research results and particularly of manufacturing "know-how."

There are presumably in the hands of the various manufacturers quite a number of patent applications on various processes for making the drug. The rights under the CMR contracts to Government will not include these manufacturing processes generally, since the latter have been carried on almost entirely at the expense of the pharmaceutical houses.

Now it may be to the public interest at the present time to bring into manufacture of this product some new group that has not contributed in any way up to the present moment. It would hardly be equitable, however, to ask the pharmaceutical houses that have borne the burden of development to make their knowledge freely available to a newcomer who is a potential competitor without compensation. However, insofar as this manufacturing knowledge is covered by patents which presumably will later call for royalty payments, the transfer of such information might be not only desirable but also equitable.

It seems, therefore, that a thorough job needs to be done very promptly of getting these manufacturers together on some basis which will adequately protect the Government interest, the public interest, and also the proper rights of the cooperating companies. I think that this can be accomplished. I feel sure that if it were accomplished the results would be very large and very satisfying.

This is the problem. It obviously needs some very careful handling. I hence told Richards today that I felt that we ought to bring in someone who knows affairs of this sort to work alongside him in the approach to this whole matter. * * * both Richards and I felt that we needed someone of very sound judgment to steer the affair and to see that it really moved toward some consummation. I have hence turned to you, and I hope very much that you will find that you can take it on.[13]

Mr. Root immediately undertook the assignment. On May 9, 1943, Root obtained from Dr. Chester S. Keefer, Medical Administrative Officer, CMR, estimates of penicillin requirements and of production, both estimates being given in units per week; and 2 days later he had separate talks with Palmer, of Squibb, and Smith, of Pfizer, about increasing production. Pfizer reported that they were producing 5 million units per week, and called priorities their greatest trouble, but indicated that they were "anxious to press ahead and increase production." Further conversations were held with representatives of Squibb and Pfizer. Following these conversations with the companies known to be most active, Root talked with Cyanamid's president, W. B. Bell, and W. G. Malcolm, of Lederle Laboratories (Amer-

[13] V. Bush to Elihu Root, Jr., April 27, 1943, records of OSRD, NA, RG 227.

ican Cyanamid), on May 19, 1943. They estimated that they could then produce in bottles 100 million units per week, and said that they expected to continue with bottle fermentation, and to be producing 300 million units per week in about 4 months. They had experimented a little with deep-vat fermentation, but with little success.

Summarizing what the companies first approached about penicillin by OSRD in October 1941, were, by late May 1943, willing to do in the way of sharing knowledge and experience, Root reported Merck and Squibb as having said that "they [would] exchange information with any reputable concern which had done hard, honest work on the subject," and that Cyanamid (Lederle), in the words of its president, "would be good sports and exchange with anybody who had done serious work." Concerning Pfizer, Root wrote: "Mr. Smith of Pfizer said that they were seriously considering the exchange of information. I got the impression that with a little urging they would come to it."[14]

In the Journal of the American Medical Association for May 22, 1943, there appeared a "Statement Released by the Committee on Medical Research" entitled "Penicillin," the first paragraph of which read as follows:

> This statement is designed to acquaint the medical profession with the progress of efforts which are being made by the Committee on Medical Research of the Office of Scientific Research and Development, by the Division of Medical Sciences of the National Research Council, and by certain commercial companies to promote investigation of the therapeutic usefulness of penicillin and to increase the available supply of this remarkable substance. They were initiated and are continuing as a phase of the war effort, directed primarily toward the benefit of our armed forces.

The discovery of penicillin by Fleming; the work of Florey, Chain, and their associates at Oxford; the studies made at the Northern Regional Research Laboratory and the continuing research there were reported, and in addition that "research looking toward production" had been going on in the laboratories of certain drug and pharmaceutical companies.

"Today," said the Committee, "some 16 companies are engaged in or intend to become engaged in the production of penicillin. In no instance has production advanced beyond the pilot-plant stage; in the majority it is still in the laboratory stage." And, it was stated further, "the difficulties which confront large scale production are very great."

What was said about clinical tests covered both the results of earlier studies and the tests—then only recently completed—at the Bushnell General Hospital, Brigham City, Utah.

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[14] Elihu Root, Jr., to A. N. Richards, May 1943, records of OSRD, NA, RG 227.

Continuing, the statement said: "The results of * * * investigations thus far have completely upheld the early promise contained in the reports of Florey, Chain, and their collaborators. More than 300 patients have been or are being treated with penicillin. There is good reason for the belief that it is far superior to any of the sulfonamides in the treatment of Staphyloccous aureus infections with and without bacteremia, * * *." Other infections in the treatment of which penicillin was reported "extremely effective" were also listed.

The statement concluded with these four brief paragraphs:

Properly made preparations have given no toxic reactions, even from the largest dosage. Its rapid excretion in the urine necessitates frequent administration when given intravenously or intramuscularly.

The work of the coming 3 months can be expected to result in clearer definition of the conditions in military medicine in which penicillin will be most useful, of its limitations and of the most advantageous as well as the most economical methods of its administration.

At the same time, intense efforts are being made by manufacturers to expand production to a point at which it may be made available in significant quantities not only for casualties returned to this country but also for our forces overseas.

Unless an expansion of production takes place at a greater rate than can now be foreseen, the supply for civilian medical needs in the near future will be exceedingly limited.[15]

The WPB Penicillin Production Program

According to an article by Fred J. Stock, Chief of WPB's Drugs and Cosmetics Branch, published in April 1945, it was "in May 1943" that "it became evident that this new drug [penicillin] would be needed by the military service in large quantities * * *. Representatives of the Drugs and Cosmetics Branch met with Dr. Richards and his associates in May 1943, and discussed the first production program."[16] This was apparently the first of the "immediate steps * * * undertaken toward an aggressive expansion of production facilities for penicillin" after "the clinical research, which had been carried on under the Office of Scientific Research and Development, showed that this new drug was dramatically effective in the treatment of certain diseases."[17]

Whether in May 1943, or later is not clear; but regarding the attitude of the industry, Stock later said:

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[15] Journal of the American Medical Association, vol. 122 (No. 4, May 22, 1943), pp. 235–236.

[16] Fred J. Stock, "Penicillin—Production and Distribution," Journal of the American Pharmaceutical Association, Practical Pharmacy Edition, Vol. VI (April 1945), p. 110.

[17] American Pharmaceutical Manufacturers Association Proceedings, midyear meeting, December 1943, p. 193.

Widespread publicity regarding the use of penicillin caused a large number of companies to investigate the possibility of producing it. More than 175 companies were interviewed or corresponded with regarding penicillin production.[18]

* * * * * * *

Twenty-one companies were selected and integrated into a program to receive priorities and such assistance as could be given by WPB. These companies were selected on the basis of their experience with penicillin, their knowledge of the production of chemicals by the fermentation method, their general experience with biological products or the processing of blood plasma and serum albumin, the technical staff, facilities available, and other pertinent factors.[19]

* * * * * * *

The Civilian Production Administration listed the following 20 companies as authorized by WPB:

Abbott Laboratories, North Chicago, Ill.
American Cyanamid Co. (Lederle), Pearl River, N. Y.
American Home Products Corp. (Wyeth),[20] Kimberton, Pa., West Chester, Pa., Philadelphia, Pa.
Ben Venue Laboratories, Bedford, Ohio.
Cheplin Biological Laboratories [20] (Bristol Laboratories, Inc.), East Syracuse, N. Y.
Cherokee Biological Laboratories, Syracuse, N. Y.
Commercial Solvents Corp., Terre Haute, Ind.
Cutter Laboratories, Berkeley, Calif.
Emerson, Sam W., and Hattie Dettleback, Cleveland, Ohio.
Heyden Chemical Corp., Princeton, N. J.
Hoffmann-La Roche, Nutley, N. J.
Eli Lilly & Co., Indianapolis, Ind.
Merck & Co., Inc., Rahway, N. J.
Merrell, William & Co. (Vick), Hamilton, Ohio.
Parke, Davis & Co., Detroit, Mich.
Chas. Pfizer & Co., Inc., Brooklyn, N. Y.
Schenley Laboratories Inc., Lawrenceburg, Ind.
E. R. Squibb & Sons, New Brunswick, N. J.
Sterling Drug Inc., Rensselaer, N. Y.
Upjohn Co., Kalamazoo, Mich.

Source: Civilian Production Administration, Industrial Statistics Division, War Industrial Facilities. Authorized July 1940–August 1945, Washington, July 30, 1946. (See also footnote to table 3, p. 54.) Albert L. Elder and Lawrence A. Monroe published in the March 1944 issue of Chemical and Metallurgical Engineering an article entitled, "Penicillin, Wartime Growing Pains of the Industry." The authors listed many of the above-named authorized companies. However, Sam W. Emerson, Hattie Dettleback, Cherokee Biological Laboratories, and Merrell, William & Co. were not included. Also, the article designated as authorized Connaught Laboratories, University of Toronto, and Ayerst, McKenna & Harrison, Montreal (a subsidiary of American Home Products Corp.) which were not mentioned in the list prepared by Civilian Production Administration.

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[18] On an earlier occasion, Stock had said: "Many of these companies were not equipped to enter commercial scale production; they did not have the facilities, personnel, or experience in the production of products similar to or related to Penicillin." (American Pharmaceutical Manufacturers Association Proceedings, midyear meeting, December 1943, p. 194.)

[19] Journal of the American Pharmaceutical Association, Practical Pharmacy Edition, vol. VI (April 1945), p. 112.

[20] American Home Products includes Reichel Laboratories purchased December 1, 1942. Bristol purchased the Cheplin plant during the war.

But it should be noted that these "companies" had been "selected" or approved to "receive such assistance as could be given by WPB." There was nothing to prevent other companies from producing if they were able to do so without assistance, though all producers were subject to the allocation order when it was issued. Thus, there were some producers other than those listed.

Once the "War Production Board came to recognize the necessity of greatly expanded facilities," as Richards commented some years later, "they surveyed the country to identify the plants most adaptable to penicillin production, saw to it that equipment was available, and through their Office of Production Research and Development obtained and distributed information that greatly increased production effectiveness." [21]

Dr. Elder, of the Chemicals Bureau, and Dr. L. A. Monroe, of the Office of Production Research and Development, discussed some of the problems of the industry as the WPB program began in an article published in March 1944. "Although," they said, "it has been established that the fundamentals of contemplated penicillin production are sound, there remains a host of problems to be solved." The most urgent of these were indicated as follows:

First is the problem of bringing all plants to full production rate. Second are those of increasing plant capacities through technological improvement to enable future increases in penicillin requirements to be met through modification of present plants so far as possible, rather than through the slower and more wasteful process of constructing new plants. Third, but perhaps most important, is the necessity to improve the quality of the product with regard to its chemical stability in order that in the future penicillin may be shipped and stored under adverse conditions without danger of deterioration.

Saying that "effort on a nationwide basis [was] being applied to the solution of the above and related problems," the authors recognized the contributions of those first concerned with penicillin production problems,[22] and then proceeded to report work initiated by the War Production Board:

Other groups brought together by the Office of Production Research and Development are also contributing technologically to the industry in the period of plant construction and conversion of processes to large scale. These include biochemists, bacteriologists, and botanists concerned with fermentation problems and working under Dr. W. H. Peterson at the University of Wisconsin; chemists, bacteriologists, and chemical engineers at the Pennsylvania State College

[21] Advances in Military Medicine, edited by E. C. Andrus, *et al.*, 2 vols., Little, Brown & Co., Boston, 1948, vol. I, p. lii.

[22] "The development in this country," it was said, "was planted and carefully tended throughout its early life by the Fermentation Division of the Northern Regional Research Laboratory of the U. S. Department of Agriculture, under the leadership of Dr. Robert D. Coghill. The work of this group, allied with the Committee on Medical Research of the Office of Scientific Research and Development, continues in its far-reaching influence over the entire field of penicillin in this country and abroad."

headed by Dean F. C. Whitmore on developing processes for the recovery of penicillin from the fermentation broth; chemical engineers headed by Dr. T. K. Sherwood at the Massachusetts Institute of Technology, studying and advising on methods of drying the final product for packaging and shipment; and plant pathologists led by Dr. E. C. Stakman at the University of Minnesota and Dr. G. W. Beadle at Stanford University in search for better mold strains. Intensive effort by corn products industry is being devoted to improvement of nutrient factors for the growth medium.[23]

By the spring of 1944, military requirements for penicillin had been met, and steps were taken to make penicillin available to the civilian population. Supplies were still limited, however. On May 1, 1944, the War Production Board established a Civilian Penicillin Distribution Unit. There were 1,000 hospitals located throughout the United States which were repositories for further distribution of penicillin in their communities.

A WPB press release dated June 28, 1944, little more than a year after the first authorizations of new plant construction under the Board's penicillin program, made two announcements which together indicated great progress in penicillin production. Regarding supplies for civilian use, the release said:

WPB * * * announced that it has approved a 20-percent increase in monthly quotas of penicillin for depot hospitals in the United States. When the plan for limited civilian distribution was made effective in the United States, it was understood that as more penicillin became available, additional hospitals would be designated as depots and, at the same time, that quotas would be raised, Chemicals Bureau representatives told the members of the Penicillin Producers Industry Advisory Committee at a recent meeting. In line with this policy, the roster has increased from the 1,000 hospitals selected in May 1944 to more than 2,000, and the July quota will reach a new high of 15 billion units which, barring unforseen emergencies, will be the regular monthly quota. Civilian depot hospitals called for 12.2 billion units of penicillin for the month of May, WPB said.[24]

The release also reported the completion of arrangements "for the export of 1 billion Oxford units of penicillin to other American Republics on an allocation for the month of June," and that plans were "being made through Foreign Economic Administration offices located in the field for a restricted worldwide distribution of the wonder drug for civilian use."

It is worth noticing here, as having contributed to the significance of the WPB's announcement just quoted, that on June 23, 1944, the OPA had issued a press release relating to penicillin prices. It said:

In response to inquiries concerning the maximum price of penicillin now available to civilian hospitals, the Office of Price Administration stated today that considerable variation in the maximum price of that material exists at the present time.

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[23] Albert L. Elder and Lawrence A. Monroe, "Penicillin, Wartime Growing Pains of the Industry," Chemical and Metallurgical Engineering, March 1944, pp. 104–105.

[24] WPB press release, June 28, 1944, NA, RG 179.

Penicillin is the relatively new medicinal agent obtained from the mold *Penicillium notatum,* used so effectively by the Army and Navy, and now available to civilian hospitals as well.

During the initial production period, costs and production conditions have varied widely, and individual manufacturers' prices were established by OPA in recognition of this variance.

OPA pointed out that actual selling prices have declined during the last year as production became greater. One seller's price to civilian hospitals is $3.15 per 100,000 Oxford units. Since some sellers are supplying the U. S. Government at a price much less than this, OPA said it is reasonable to expect further reductions in the price to civilian hospitals.[25]

Early in February 1945, the WPB reported that "production in December 1944 was 278 billion units (2,780,000 vials), while the January 1945 production was approximately 330 billion units (3,300,000 vials), as compared with an output of 12,500 million units in January 1944," and that "a 20-percent increase in monthly quotas of penicillin for more than 2,700 depot hospitals [had] been in effect since February 1." [26]

A month later, WPB announced that as of March 15, 1945, "producers and distributors" would be permitted to sell penicillin "through normal trade channels * * * in vials containing 100,000 units of sodium penicillin for human parenteral medication." Authorized to be sold from March 15 to March 31 were 1,280,000 vials, while "an additional quantity of approximately 1,500,000 vials" was to "be made available for distribution in April." After March 15, the 2,700 depot hospitals could obtain supplies through distributors. Although supplies were not yet sufficient to permit the manufacture of any but the parenteral dosage form,[27] large-scale commercial production of penicillin had become a reality.

By 1946 the rising production permitted the inclusion of pencillin in formal CPA allocations. In the initial allocation in 1946 there was a final allocation total of 32,690.63 billion Oxford units. Civilian allocations in parenteral, bulk, and dosage forms took more than half with a total of 16,614.74 billion Oxford units. The military allocation was a surprisingly small total of 2,000 billion Oxford units.

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[25] OPA advance release for Friday afternoon papers, June 23, 1944, NA, RG 188.
[26] WPB press release, February 8, 1945, NA, RG 179.
[27] WPB advance release for Thursday morning papers, March 8, 1945, NA, RG 179.

CHAPTER II

The Influence of National Defense on the Development of the Antibiotics Industry

Although the manufacture of antibiotics is frequently referred to as an industry, it really is only a segment of the larger pharmaceutical industry. This segment is distinguished by the use of biosynthetic chemical processes of fermentation in which some kinds of living micro-organisms act as catalytic agents to produce inanimate chemical substances capable of destroying or inhibiting the growth of other living micro-organisms. Most antibiotics are produced by direct fermentation. Today, however, one antibiotic, chloramphenicol, which can be produced by fermentation, is produced commercially by chemical synthesis. Another, tetracycline, can be produced directly by fermentation, or by catalytic reduction of chlortetracycline which in turn is produced by fermentation. Streptomycin, produced by fermentation, may be further processed into dihydrostreptomycin.

In chapter I, the story of the discovery and development of penicillin was presented. Put into production during World War II, this first antibiotic brought the world a new weapon against infections and diseases. Perhaps of even more significance, in the long range, was the impetus given to a new phase of the study of micro-organisms—whose full potentialities are still far from known. In this chapter, the role of wartime planning and Government spending in the development of the antibiotics industry will be discussed. The participation of private industry in this program also will be considered. Public funds will be the first aspect analyzed.

World War II

Both private and public interest in the production of penicillin was greatly stimulated when Messrs. Florey and Heatley visited the United States in July 1941. Prior to this date, the Northern Regional Research Laboratory of the United States Department of Agriculture at Peoria, Ill., was engaged in mold research, and the Committee on Medical Research had been set up in the Office of Scientific Research and Development in June 1941. Thus these two Government agencies were in a position to receive the British visitors. In August 1941, Florey

visited several American and Canadian companies which already were producing drugs and chemicals by fermentation processes. His purpose was to induce them to produce penicillin. Some of these companies already were carrying on laboratory research respecting penicillin, but neither public nor private research had yet developed the information needed for setting up commercial production. Following this visit, further research was continued by both Government agencies and private companies. Part of this research was financed with public funds, and the remainder was financed by private interests.

Before study of penicillin could be seriously undertaken, supplies of the material had to be obtained. Companies which had experienced research teams and which had obtained some penicillin in experimental work were asked to contribute all of their penicillin to the Government for use in a research program. With this penicillin, the Government launched an intensive program of research.

Public funds expended for research

World War II records examined by the Commission's staff do not indicate the total amount of public funds spent by Government agencies on penicillin or other antibiotics research which they conducted themselves. Available records of the Office of Scientific Research and Development, however, indicate that it entered into numerous contracts with nongovernmental agencies and a few with other Federal or local government agencies. Among these were contracts under which varying amounts of public funds were contributed toward research by universities, hospitals, and other private or semiprivate agencies into penicillin's chemical structure and its use in therapy. The amounts varied greatly among the agencies assisted as well as with the objectives of research.

A list of such projects appearing in volume II of Advances in Military Medicine, published in 1948, indicates that at least 56 such contracts covering research in penicillin or its use in treatment of diseases were made by the Office of Scientific Research and Development during World War II. Of these contracts, nine were with pharmaceutical manufacturers, and involved no grants of public funds. Of the remaining 47 contracts, 36 were with educational institutions, 6 were with hospitals, 2 were with other Federal Government agencies, and 3 were, respectively, with the Chicago Board of Health, Merck Institute, and the National Academy of Sciences. Two of the contracts related to development of streptomycin, while all the others related to penicillin. The total amount of public funds granted under these contracts was $2,770,305. The list of contracting parties, the subjects of their research, and the amounts granted under each contract as shown by the records of the Office of Scientific Research and Development examined are shown in table 1 below.

TABLE 1.—*Antibiotics research contracts concluded by the Office of Scientific Research and Development during World War II*

Contractor	Contract No.[1]	Subject of research (short title)	Cost to Government
Bradley Polytechnic	100	Cultural Methods and Assay of Penicillin	$27,121.85
Princeton University	119	Method for Quick Titration of Potency of Penicillin	3,000.00
St. Louis University	155	Discovery of Products Superior to Penicillin and Pyocyanase	2,001.00
Massachusetts Memorial Hospitals	275	Collection and Coordination of Information Concerning Penicillin	1,834,444.70
University of Buffalo	359	Penicillin Therapy of War Wounds	3,408.09
E. R. Squibb & Sons	389	Chemical Structure and Synthesis of Penicillin	(2)
Chas. Pfizer & Co., Inc	390	do	(2)
Merck & Co., Inc	391	do	(2)
Johns Hopkins University	393	Effect of Penicillin in Syphilis	91,434.50
Abbott Laboratories	396	Chemical Structure and Synthesis of Penicillin	(2)
Eli Lilly & Co	397	do	(2)
Parke, Davis & Co	398	do	(2)
The Upjohn Co	399	do	(2)
University of Pennsylvania	403	Effect of Penicillin on Syphilis	100,898.00
New York University	404	Treatment of Early Syphilis With Penicillin	61,057.00
University of Michigan	408	Chemical Structure and Synthesis of Penicillin	68,040.13
U. S. Department of Agriculture	410	Chemical Structure of Penicillin	[3] 46,483.00
Cornell University	411	Chemical Structure and Synthesis of Penicillin	162,112.53
University of Illinois	426	Value of Penicillin in Treatment of Compound Fractures	6,125.00
Tufts College	427	Treatment of Compound Fractures With Prophylactic Penicillin Therapy	17,223.90
Winthrop Chemical Co. / Heyden Chemical Corp	428	Chemical Structure and Synthesis of Penicillin	(2)
University of California	431	Use of Penicillin in Infections, Especially Craniocerebral Infection	16,792.12
Cornell University	435	Effectiveness of Penicillin Therapy in Syphilis	14,407.46
University of Illinois	439	Structure of Penicillin and Related Compounds	8,689.25
University of Michigan	442	Infrared Pictures of Penicillin Crystals	39,892.16
Shell Development Co. / Cutter Laboratories	445	Chemical Structure and Synthesis of Penicillin	(2)
Duke University	446	Penicillin Treatment for Syphilis	5,725.15
Hospital for Joint Diseases	457	Use of Penicillin in the Therapy of Hematogenous Osteomyelitis	6,500.00
Washington University	460	Effect of Penicillin on Character and Severity of Bacterial Infections	3,210.08
Tulane University	461	Treatment of Congenital Syphilis With Penicillin	5,250.00
Vanderbilt University	462	Clinical Value of Penicillin in Various Infectious Conditions	6,092.00
Food and Drug Administration	465	Improvement in Assay Procedures Used in Control of Penicillin	(4)
Mount Sinai Hospital	479	Penicillin Therapy of Subacute Bacterial Endocarditis	3,525.00
Wills Hospital, Philadelphia	480	Penicillin Treatment of Ocular Syphilis	1,462.00
University of Virginia	495	Penicillin in the Treatment of Syphilis	4,008.00
University of Texas	496	Use of Penicillin in Treatment of Syphilis, Acquired and Congenital	10,863.00
Western Reserve University	497	Penicillin Therapy of Syphilis	7,842.03
University of Chicago	501	Effects of Penicillin Therapy on Central Nervous System	3,511.75
Vanderbilt University	505	Effectiveness of Penicillin in Treatment of Syphilis	1,612.94
Chicago Board of Health	510	Penicillin in Venereal Disease (Syphilis)	49,444.32
Wayne University	511	Penicillin Therapy of Syphilis	8,352.93

Stanford University	514	Treatment of Early Syphilis with Penicillin	6, 249. 94
University of Michigan	515	Penicillin Therapy for Early and Late Syphilis	4, 325. 00
Washington University	519	Treatment of Early Syphilis With Penicillin	5, 697. 25
University of California	520	Penicillin Treatment of Subacute Bacterial Endocarditis	2, 252. 89
Johns Hopkins University	526	Efficacy of Derivatives From Penicillin in Treatment of Experimental Syphilis	4, 465. 00
Do	527	Biostatical Analysis of Nationwide Results of Penicillin Therapy in Syphilis	33, 737. 00
Harvard University	540	Chemical Structure and Synthesis of Penicillin	13, 546. 83
Cornell University	542	Compilation of Chemical Index in Connection With Patent Questions	11, 520. 00
Merck Institute	544	Properties of Streptomycin	1. 00
Washington University	551	Pharmalogic and Toxicologic Study of Streptomycin	1, 333. 95
St. Louis University	553	Discovery and Development of Products Superior to Penicillin and Pyocyanase	1. 00
New Britain General Hospital	558	Penicillin and Other Antibiotic Agents in Experimental Syphilis	9, 765. 23
Stanford University	561	Penicillin Biosynthesis and Inactivation in Culture	17, 704. 00
Massachusetts Memorial Hospitals	569	Prepare Material for a Monograph on Penicillin	9, 176. 48
National Academy of Sciences	571	Prepare Monograph on Work Done Under U. S. and U. K. Sponsorship on Penicillin	30, 000. 00
Total			2, 770, 305. 46

[1] OEMcmr series.
[2] No cost to the Government.
[3] This sum represents a transfer between Government agencies.
[4] Not available.

Source: Advances in Military Medicines, vol. II, E. C. Andrus et al., eds., Little, Brown & Co., Boston, 1948, pp. 831 ff.; Records of OSRD, NA, RG 227, National Archives, Washington, D. C.

In relation to the above table, it may also be noted that the Department of Agriculture launched a $100,000 penicillin project at the Northern Regional Research Laboratory in Peoria, Ill.[1] Between 1942 and 1944 the OSRD turned over more than $27,000 to the Bradley Polytechnic Institute in Peoria to permit its participation in the work being done at the Northern Laboratory.[2]

The pharmaceutical companies which carried on research into penicillin's chemical structure, and the possibility of its synthesis, under contract with the Office of Scientific Research and Development did so entirely at their own expense. The educational institutions in most instances devoted their efforts under their contracts to clinical testing of penicillin, for which payment was made by the Government.

It appears that several pharmaceutical firms had been experimenting with penicillin, and, after meetings called by the Government in October and December 1941, an agreement was reached whereby the companies contributed whatever penicillin they could produce to the Committee for distribution to designated physician investigators. The companies continued their research at their own expense in accordance with this agreement until in February 1943 the Office of Scientific Research and Development began paying them for the penicillin they were able to produce and contribute to the testing program. The final purchase cost to the Government was about $2 million.[3]

These arrangements made it possible for laboratory and clinical tests to proceed at the same time that methods of production were being studied by both the Government and prospective producers. Production at first was on a laboratory scale, but this experience laid the basis for subsequent production on a commercial scale. As a result of these combined efforts, the first patient was treated on March 14, 1942. The first soldiers were treated with penicillin in April 1943 at the Bushnell General Hospital in Brigham City, Utah. By the summer of 1943, 209 cases had been treated in 11 Army hospitals and it had been shown that penicillin was effective against infections caused by staphylococci, streptococci, pneumococci, meningococci, and gonococci microorganisms. By June 1944 the Army and Navy had adopted penicillin as routine treatment for syphilis,[4] and supplies of penicillin were becoming a practical reality.

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[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

[2] Kenneth B. Raper, "Research in the Development of Penicillin," Advances in Military Medicine, vol. II, Little, Brown & Co., Boston, 1948, pp. 725, 726.

[3] James Phinney Baxter 3d, Scientists Against Time, Little, Brown & Co., Boston, 1950, p. 352.

[4] Ibid., p. 358.

The 56 contracts were executed in 1943 and the program concluded in 1945. An important feature of their operation was that all the participants made regular reports on their progress to the Committee on Medical Research of the Office of Scientific Research and Development. The Committee, in turn, provided each contractor with copies of reports. The pharmaceutical companies received no direct payment from the Government. They did, however, benefit from participation in the interchange of technical knowledge.

Government-financed plants

As soon as it appeared feasible to manufacture penicillin, the Office of Scientific Research and Development, in cooperation with the War Production Board, took steps to arrange for the construction of plants necessary to provide wartime requirements for penicillin.[5] The first penicillin production units were financed by the Government and operated by 6 pharmaceutical companies, which later purchased the 6 facilities as surplus war property. Such Government-financed plants were described by the Surplus Property Administrator after the war as "scrambled facilities," consisting of equipment and usually some construction, such as a wing added to a privately owned factory, an enlargement of a building, or the erection of a single building in the middle of a group of privately owned buildings.[6]

Some of these plants included facilities for production of wartime medicines other than penicillin. The expenditures for penicillin facilities were reported (table 3, pp. 54–55) as $7,577, 697 in addition to company expenditures of $2,859,567, which represented expenditures for power plants, packaging machinery, and certain minor purposes at the plants operated by Abbott Laboratories and American Cyanamid. It is reported that the Government recovered $3,352,724 by sale of these facilities after World War II to the companies that had operated them. On this basis, the cost of these facilities to the Government was $4,224,973.[7]

Table 2 below presents data covering the names of purchasers of the Government-financed antibiotics plants, and Government's original expenditure and the amounts recovered by the sale of each of the 6 plants (Plancors).

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[5] Kenneth B. Raper, "Research in the Development of Penicillin," Advances in Military Medicine, vol. II, Little, Brown & Co., Boston, 1948, p. 727; James Phinney Baxter 3d, Scientists Against Time, Little, Brown & Co., Boston, 1950, p. 349.

[6] "The Liquidation of War Surpluses," quarterly progress report to the Congress by the Surplus Property Administration, 4th Quarter, 1945, p. 19.

[7] The disposal agency listed the cost to the Government of these facilities as $7,918,698, and on this basis, the cost to the Government would be increased accordingly.

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TABLE 2.—*Public funds expended and amounts recovered by the sale of 6 World War II penicillin plants*

Purchases and location of plants	Plancor No.[1]	Government expenditure [2]	Reported sales price	
			Amount	Percent of cost to Government
Abbott Laboratories, North Chicago, Ill	2271	$197,497	$136,258	69.0
American Cyanamid Co., Pearl River, N. Y	1937	784,528	91,366	11.6
Ben Venue Laboratories, Bedford, Ohio	1942	335,672	150,000	44.7
Bristol Laboratories, Inc., East Syracuse, N. Y	1935	2,410,000	1,100,100	45.6
Cutter Laboratories, Berkeley, Calif	1926	850,000	175,000	20.6
Heyden Chemical Corp.,[3] Princeton, N. J	1951	3,000,000	1,700,000	56.7
Total, 6 plants		7,577,697	3,352,724	44.2

[1] Numbers assigned by the Reconstruction Finance Corporation to plants in the program of the Defense Plants Corporation.
[2] From table 3 on pp. 54–55
[3] This plant was used for the production of formaldehyde and hexamine in addition to penicillin.
Source: War Assets Administration, Office of Real Property Disposal, Sales and Leases of Industrial, Transportation, and Maritime Property as of June 30, 1947, Washington, D. C.
Records of the Reconstruction Finance Corporation, NA, RG 234, National Archives, Washington, D. C.
General Services Administration, Public Buildings Service, Surplus Industrial Real Property and Related Personal Property, Sales and Transfers as of Sept. 30, 1952, Washington, D. C.
Annual reports of antibiotics manufacturers.

Private plant construction

The penicillin plant construction program was not limited to the six production units which were financed by the Government. In May 1943 the War Production Board prepared the way for construction of additional plants by private industry. Along with AA–1 priorities for the purchase of equipment (covered by certificates of necessity issued by the Government), the program gave industry a further inducement to undertake construction of plants. This was a tax provision which permitted the companies to amortize these defense facilities in a 5-year or shorter period rather than over the normal amortization period that applied to chemical plants—usually 12 to 15 years. Some of the antibiotics manufacturers did not use this privilege, electing instead to take the normal depreciation period; others obtained permission to amortize depreciation in less than 5 years.

In all, 22 antibiotics facilities were authorized under the wartime program, including the 6 initial units financed by the Government. The 20 companies authorized to participate in the World War II antibiotics program, and the plants covered by the authorizations, are listed in table 3. These facilities included 20 penicillin production units, 1 penicillin research unit, and 1 streptomycin pilot plant. These facilities were not, in most cases, entire plants. Some of them merely represented additions to plants already experimenting with antibiotics production. From such data as are available, it appears that the total estimated cost of war time plants to be built with private funds amounted to $22,640,670. As previously indicated, the Government expended $7,577,697 for plants. Thus, total of private and public funds authorized for new plant expenditures during World War II was $30,218,367. Of this amount, funds contributed initially by the Government represented about 25 percent. This intensive plant construction program proceeded despite the general belief that penicil-

lin production by chemical synthesis would soon replace the use of molds. Instead, it was found possible to produce penicillin in great volume through the growth of molds.

World War II treatment of plant investment risks

The emergency nature of the project, newness of the product penicillin, lack of established technique for its production, and the fact that the best types of equipment had not yet been developed and that research was still going on which might very rapidly make production facilities obsolete—all were factors creating risks in the investment of funds in new plant facilities.

For these reasons expenditures on plants or portions of plants built with private funds were authorized for rapid tax amortization (accelerated depreciation). In practice, the companies were granted 100-percent rapid tax amortization privileges for their privately financed facilities which it is believed would be relatively useless after the war. Thirty-five percent writeoffs were given for equipment that was regarded by the War Production Board as being salvageable, whether or not production methods were changed.[8] Also, in 1944, when deep-tank production became feasible, the Government allowed rapid amortization on 50 percent of the cost of equipment installed in converting from the bottle method to the deep-tank method of fermentation.[9]

The combined result of the Government's plant-building program, high priorities for materials, and the granting of fast amortization on private capital invested, was rapid expansion of production facilities which enabled the industry to deliver penicillin in some quantity within a comparatively short time. The Government program more than overcame any deterrent that might have arisen from the knowledge that the facilities would soon be obsolete as a result of technological advances.

Data furnished by the companies in response to schedule VIII of the Commission's 1957 request for information, supplemented by data compiled by the Civilian Production Administration in 1946, indicates that 14 companies obtained rapid tax amortization privileges amounting to $14,464,962, on a total investment of $22,640,670 of their own funds in wartime plants. Included in this total are facilities listed as having been authorized during the war which apparently were not approved for rapid tax amortization. Expenditure for these facilities totaled $526,000.

Table 3 lists the 20 companies which operated the 22 World War II facilities, and lists the amounts of Government expenditure and private investments, and the amounts authorized for rapid tax amortization out of privately invested funds for each plant.

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[8] Memorandum from Wm. G. Hughes, Drugs and Penicillin Facilities Unit, War Production Board, to Tax Amortization Branch, War Production Board, dated July 8, 1944, records of the War Production Board, NA, RG 179, Washington.

[9] "Conference Report in Tax Amortization Percentage Relative to Facility Expansion of Penicillin Plants," records of the War Production Board, NA, RG 179, Washington.

Table 3.—*Antibiotics facilities authorized during 1943–45*

Name of applicant—location of facilities	Type of facility: Production	Type of facility: Other	Total cost	Public funds	Private funds	Percentage of private funds authorized for rapid amortization	Amount approved for rapid tax amortization	Facilities completed (year)
Abbott Laboratories, North Chicago, Ill.	Penicillin		$670,704	$197,497	$473,207	100.0	$473,207	1944–45
American Cyanamid Co. (Lederle), PearlRiver, N. Y.	do		3,170,888	784,528	2,386,360	87.0	2,075,230	1944–45
American Home Products Corp. (Wyeth):[1]								
Kimberton, Pa.	do		470,082		470,082	99.4	467,216	1943–45
West Chester, Pa.	do		506,322		506,322	85.3	431,962	1943–45
Philadelphia, Pa.	do	Research penicillin.	280,000		280,000			
Ben Venue Laboratories, Bedford, Ohio.	do		335,672	335,672				1944
Bristol Laboratories, Inc., East Syracuse, N. Y.	do		2,410,000	2,410,000				1944
Cherokee Biological Laboratories,[2] Syracuse, N. Y.	do		210,000		210,000			n. a.
Commercial Solvents Corp., Terre Haute, Ind.	do		1,869,000		1,869,000	97.2	1,817,000	1944
Cutter Laboratories, Berkeley, Calif.	do		850,000	850,000				1944
Emerson, Sam W., and Hattie Dettleback,[2] Cleveland, Ohio.	do		36,000		36,000			n. a.
Heyden Chemical Corp., Princeton, N. J.	do		3,000,000	3,000,000				1943
Hoffmann LaRoche, Nutley, N. J.	Penicillin, ascorbic acid, thiamine chloride, riboflavin, synthetic vitamins.		1,935,000		1,935,000	66.2	1,281,000	n. a.
Eli Lilly & Co., Indianapolis, Ind.	Penicillin		710,880		710,880	77.1	548,079	1944–45
Merck & Co., Inc , Rahway, N. J.	Penicillin, thiamine hydrochloride, synthetic papaverine, sulfathizole, sodamide, ascorbic acid, acetylaminobenzene, sulfomyl chloride, niacinamide, riboflavin, vitamin B–6, sulfapyridine, atabrine, cadeine, dichlorodiphenyl, trichlorethane, flour-enriched tablets.		5,749,000		5,749,000	4.8	276,000	n. a.
Merrell, William & Co. (Vick),[2] Hamilton, Ohio.		Pilot plant—streptomycin.	65,000		65,000	100.0	65,000	n. a.
Parke, Davis & Co., Detroit, Mich.	Penicillin, epidermic typhus vaccine, gelatine capsules, influenza virus vaccine.		789,000		789,000	60.8	480,000	n. a.

Chas. Pfizer & Co., Inc., Brooklyn, N. Y.	Penicillin		3, 396, 902		3, 396, 902	92. 8	3, 151, 396	1944–45
Schenley Laboratories Inc., Lawrenceburg, Ind.	do		1, 175, 174		1, 175, 174	100. 0	1, 175, 174	1943–45
E. R. Squibb & Sons,[3] New Brunswick, N. J.	do		2, 107, 615		2, 107, 615	88. 9	1, 874, 128	1945
Sterling Drug, Inc., Rensselaer, N. Y.	Penicillin, atabrine, and sulfathiazole		157, 000		157, 000	51. 0	80, 000	n. a.
Upjohn Co., Kalamazoo, Mich	Penicillin		324, 128		324, 128	83. 2	269, 590	1944–45
Total			30, 218, 367	7, 577, 697	22, 640, 670	63. 9	14, 464, 982	

"n. a." indicates that data are "not available."
[1] Includes Reichel Laboratories purchased by American Home Products, Dec. 1, 1942.
[2] See source note, ch. I, to Civilian Production Administration list of companies authorized to receive priority assistance.
[3] Merged with Olin Mathieson in 1952.

Source: FTC data request 1957, schedule VIII, and Civilian Production Administration, Industrial Statistics Division, War Industrial Facilities Authorized, July 1940–August 1945, Washington, July 30, 1946.

The percentages of private investment on which accelerated amortization was granted varied from project to project, but were high enough to indicate that a large part of the facilities were regarded as having little salvage value after the war. Of the 18 facilities on which private funds were used, 10 authorizations for accelerated tax amortizations covered over 80 percent of the private funds invested, as against 4 falling between 50 and 80 percent, and only 1 falling below 50 percent. The Merck plant, only a small part of which was devoted to penicillin, received a low (4.8 percent) rating for accelerated depreciation.

Growth Between World War II and the Korean War

Increasing civilian use of penicillin provided a demand capable of more than counterbalancing decreased demand for military use following the cessation of hostilities in World War II. The result was that antibiotics manufacturers were willing to invest additional funds in production facilities. The penicillin facilities in which public funds had been invested during the war were purchased by the companies that had operated them at that time. These six older, flask-type units were either modernized by the companies or, as in the case of Cutter and Ben Venue, production was ultimately dropped. In addition, these companies and other chemical and pharmaceutical companies expended additional private funds in building entirely new facilities, or expanding capacity in existing ones. Part of this postwar expansion was accomplished by the purchase or lease of four surplus war plants, originally built for other purposes and converting them to antibiotics production. Amounts expended for conversion of these facilities are not available for all companies.

In this last category is Eli Lilly's purchase of a portion of Plancor 44, an airplane propeller plant, built by the Government at a cost of $5,941,968 and operated during the war by Curtiss-Wright Corp. Lily paid $2,500,000 for part of this wartime plant and converted the facilities to penicillin production.[10] Pfizer purchased Navy plant 164 at Groton, Conn., which had been constructed by the Government at a cost of $5,285,538 and operated by the Electric Boat Co., as a submarine repair base during the war. This plant, which cost Pfizer $919,500, was converted to penicillin production.[11]

Pfizer also leased a surplus ammunition loading plant at Terre Haute, called the Vigo Ordnance Plant, for 20 years at a rental of $200,000 per year. This plant contained 648 buildings on 6,146 acres of land [12] and is now used for the manufacture and packaging of antibiotics. Merck purchased, for $862,500, a portion of the Cherokee Ordnance Works plant (War No. 45) at Danville, Pa., for conversion to antibiotics production. These four surplus plants which were con-

[10] Office of Real Property Disposal, War Assets Administration, Sale and Leases of Industrial Transportation, and Maritime Real Property, as of June 30, 1947, Washington, p. 12.
[11] Ibid., p. 14.
[12] Office of Real Property Disposal, War Assets Administration, Plant Finder, Washington, February 1948, p. 16.

verted to antibiotics production are still being operated by Merck, Lilly, and Pfizer.

In all, antibiotics manufacturers purchased or leased 10 surplus war facilities for a total of over $11.6 million, representing an estimated 45 percent of the Government outlay for the plants. This return to the Government was not far out of line with the realization from the overall surplus plant disposal program at that time. The Government had recovered, by September of 1947, for the 1,238 plants disposed of as surplus an average of just under 45 percent of the original cost.[13]

Throughout the period from 1946 to 1950, the demand for antibiotics for domestic use and export grew steadily. In 1948, the list of antibiotics substances reported as being in production included five types of penicillin, streptomycin, dihydrostreptomycin, bacitracin, chlortetracycline, and chloramphenicol; in 1949, tyrothricin was added, and in 1950 oxytetracycline and viomycin were added. Throughout these years, the antibiotics produced in largest volumes were penicillin and the two streptomycins. Also, production of two of the newer broad spectrums, chlortetracycline and chloramphenicol, was growing rapidly.

The Korean War

Penicillin again became an important wartime item in June 1950 at the time of the Korean action. Expansion Goal No. 129 (penicillin) was originally established by the Government at 250,000 billion units a year, but by the middle of 1952 this goal had been increased to 600,000 billion units a year, the target date for accomplishment of this output was January 1, 1955.[14]

Under Goal No. 129, certificates of necessity were issued to applicants who had recently begun expansion of antibiotics facilities or who were willing to undertake plant expansions. Facilities for production of chlortetracycline, oxytetracycline, streptomycin, and bacitracin were authorized as well as penicillin since, as explained by industry, these facilities could be readily converted to penicillin production in the event that the war situation demanded it.

Under this program, the Government authorized the expenditure of over $110 million in expanding production facilities of penicillin and other antibiotics. This expenditure, all by private industry, represented 0.3 percent of the total defense expansion program. Nearly 57 percent (or $62,796,416) of the antibiotics construction was approved for rapid depreciation. Certificates of necessity were issued to 16 companies covering 35 plant alterations, conversions, or expansions. Fourteen applications under Goal 129 were withdrawn or denied. In all, 22 plants were modernized and expanded under this program. Table 4 lists the antibiotics facilities authorized under Goal 129.

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[13] War Assets Administration, Report on Government-Owned Industrial Plants as of September 30, 1947, April 1948, pp. 5 and 9.

[14] Defense Production Administration Directive dated June 30, 1952, entitled, "Expansion Goal No. 129"; Defense Production Administration Release DPA-388, dated July 14, 1952.

TABLE 4.—*Antibiotics facilities authorized during 1950–53*

Name of applicant—location of facilities	CN-TA application No.	CN-TA application date	CN-TA application denied or withdrawn	Type of facility: Production	Type of facility: Package or storage	Type of facility: Other	Total authorized expenditures	Rate (percent) approved for rapid tax amortization	Amount approved for rapid tax amortization	Facilities completed (year)
Abbott Laboratories							$1,854,014		$1,069,656	
North Chicago, Ill	3357	Feb. 14, 1951		Penicillin			1,569,000	60	941,400	1953
Do	5799	n. a.				Power plant	285,014	45	128,256	1952
Do	19627	Apr. 4, 1952	Oct. 16, 1952		Penicillin					
American Cyanamid Co. (Lederle):							27,196,180		15,544,716	
Pearl River, N. Y	1559	Jan. 11, 1951		Chlortetracycline			6,498,000	60	3,898,800	1953
Do	6344	Mar. 22, 1951			Chlortetracycline.		5,153,280	[1] 45	2,318,976	1954
Willow Island, W. Va	3545	Feb. 26, 1951		Chlortetracycline			9,707,000	60	5,824,200	1953
Princeton, N. J.[2]	3379	Feb. 26, 1951		Penicillin, streptomycin.			5,837,900	60	3,502,740	n. a.
American Home Products (Wyeth):							4,547,000		2,358,600	
West Chester, Pa	21374	June 2, 1952		Penicillin			4,547,000	30, 45, 60	2,358,600	1954
Bristol Laboratories							2,824,000		1,835,600	
East Syracuse, N. Y	3104	Feb. 15, 1951		Penicillin			2,824,000	65	1,835,600	1953
Do	15259	Oct. 26, 1951	June 28, 1954	Penicillin, dihydrostreptomycin.	Penicillin					
Do	18623	Feb. 26, 1952	June 29, 1954	Penicillin, streptomycin.						
Commercial Solvents Corp							2,470,450		1,539,397	
Terre Haute, Ind	12297	Jan. 12, 1951		Bacitracin			26,450	55	14,547	n. a.
Do	5815	Mar. 20, 1951		do			802,000	65	521,300	1951
Do	5816	Mar. 20, 1951		Penicillin			1,217,000	65	791,050	1952
Do	14756	Sept. 28, 1951			Penicillin		425,000	50	212,500	1952
Corn Products Refining Co										
Pekin, Ill	10441	June 11, 1951	Feb. 26, 1952	Corn steep for antibiotics.						
Cutter Laboratories							104,000		72,800	
Berkeley, Calif	1585	Jan. 5, 1951		Penicillin			104,000	70	72,800	1952
Kilbane Bros., Inc										
North Chicago, Ill	13269	July 27, 1951	Apr. 21, 1952		Antibiotics					

Eli Lilly & Co.							22, 874, 000		12, 000, 550	
Indianapolis, Ind.	5794	Mar. 15, 1951		Penicillin, streptomycin and vitamin B-12.			4, 910, 000	60	2, 946, 000	1952
Do.	19884	Apr. 22, 1952		do			1, 451, 000	55	798, 050	1953
Lafayette, Ind.	9530	May 21, 1951		Penicillin, streptomycin.			16, 513, 000	50	8, 256, 500	1953
Merck & Co.							7, 887, 000		4, 632, 400	
Danville, Pa.	5336	Mar. 21, 1951		Penicillin			6, 889, 000	60	4, 133, 400	1952
Do.	11058	June 14, 1951			Cortisone, dihydrostreptomycin, penicillin.		998, 000	50	499, 000	1953
Monsanto Chemical Co.							1, 682, 000		763, 200	
St. Louis, Mo.	6124	Mar. 23, 1951		Chloramphenicol			1, 230, 000	40	492, 000	1954
Do.	11410	June 12, 1951		Chloramphenicol, intermediate.			77, 000	60	46, 200	1951
Monsanto, Ill.	7622	June 12, 1951		do			375, 000	60	225, 000	1952
Everett, Mass.	11348	June 14, 1951	Nov. 19, 1951	Vitamin B-12						
Novocol Chemical Manufacturing Co.							97. 000		48, 500	
Brooklyn 7, N. Y.	1870	Jan. 15, 1951			Penicillin		97, 000	50	48. 500	1951
Parke, Davis & Co.							3, 971, 000		2, 382, 600	
Holland, Mich.	2845	Feb. 5, 1951		Chloramphenicol			3, 971, 000	60	2, 382, 600	1952
Detroit, Mich.	10468	June 8, 1951	Oct. 24, 1952	Penicillin—S. R.						
S. B. Penick & Co.										
Newark 5, N. J.	16165	Nov. 14, 1951	Apr. 28, 1952	Bacitracin						
Chas. Pfizer & Co., Inc.							19, 233, 202		11, 766, 647	
Groton, Conn.	1247	Dec. 27, 1950		Penicillin, streptomycin, oxytetracycline.			7, 708, 279	65	5, 010, 381	1954
Do.	11372	June 8, 1951		do			7, 945, 657	60	4, 767, 394	1954
Do.	11452	Dec. 10, 1951	Sept. 9, 1952	Antibiotics by organic synthesis (penicillin, streptomycin, (oxytetracycline).						
Brooklyn, N. Y.	1248	Dec. 29, 1950					895, 542	65	582, 102	1952
Do.	11371	June 11, 1951			Penicillin, streptomycin, oxytetracycline.		2, 251, 000	50	1, 125, 500	1954
Do.	26902	Oct. 9, 1953	Jan. 25, 1954			Administration Building.				

See footnotes at end of table.

TABLE 4.—*Antibiotics facilities authorized during 1950–53*—Continued

Name of applicant—location of facilities	CN-TA application No.	CN-TA application date	CN-TA application denied or withdrawn	Type of facility: Production	Type of facility: Package or storage	Type of facility: Other	Total authorized expenditures	Rate (percent) approved for rapid tax amortization	Amount approved for rapid tax amortization	Facilities completed (year)
Chas. Pfizer & Co., Inc.—Con. Terre Haute, Ind.	1249	Jan. 2, 1951		Streptomycin, oxytetracycline.			$432,724	65	$281,270	1951
Do	18780	Feb. 25, 1952	July 2, 1952	Terralac, Feed supplement.						
Publicker Industries, Inc.										
Philadelphia 2, Pa.	20991	June 12, 1952	Oct. 2, 1952	Penicillin, bacitracin, vitamin B-12.						
Schenley Laboratories, Inc.							185,652		120,673	
Lawrenceburg, Ind.	8076	Apr. 10, 1951		Penicillin, streptomycin.			185,652	65	120,673	1953
E. R. Squibb & Sons,[3] (Olin Mathieson).							11,649,193		6,753,208	
New Brunswick, N. J.	720	Dec. 17, 1950		Penicillin, streptomycin.			3,470,871	60	2,082,522	1951
Do	11363	June 14, 1951		do			1,697,000	60	1,018,200	1952
Do	15357	Oct. 30, 1951		do			4,811,322	45/60	2,650,486	1955
Do	18506	Feb. 25, 1952		do			1,670,000	60	1,002,000	1955
São Paulo, Brazil	14988	Oct. 9, 1951	Oct. 29, 1952	Penicillin, streptomycin, vitamin B-12.						
The Upjohn Co.							3,465,000		1,732,500	
Kalamazoo, Mich.	9247	May 16, 1951		Penicillin, other antibiotics.			3,465,000	50	1,732,500	1954
Do	14013	Aug. 22, 1951	Apr. 21, 1952			Medical research.				
Vick Chemical Co. (J. T. Baker Co.).							250,528		175,369	
Phillipsburg, N. J.	1957	Jan. 23, 1951		Penicillin			250,528	70	175,369	1952
Total							110,290,219		62,796,416	

[1] This rate applies to 44 percent of the total construction ($11,712,000) or $5,153,280—the portion of construction relating to chlortetracycline.
[2] Purchased from Heyden Chemical Corp., on Dec. 1, 1953.
[3] Merged with Olin Mathieson in 1952.

Source: Compiled from records of the Office of Defense Mobilization, 1956.

Highlights of Government Emergency Program

The penicillin program was launched during World War II with a total Federal expenditure of about $13 million (of which about $7,577,000 was for plants and the remainder was for research and research materials),[15] and an expenditure by private industry of about $22,600,000 for plant and equipment. About 65 percent ($14,500,000) of the private expenditure was allowed for rapid tax amortization.

Antibiotics were sent abroad under several foreign assistance programs. The first shipments of penicillin began in 1944 under the lend-lease program.[16] Later, about 5,000 billion units of penicillin were distributed to war-devastated areas by the United Nations from United States stocks.[17] These shipments began in 1946 and included some streptomycin which was needed because of an alarming increase in tuberculosis.[18]

The United States also arranged through the United Nations for the export of 7 penicillin plants, each designed to produce about 50 billion units of penicillin a month. Plants were sent to China, Czechoslovakia, Italy, Poland, Byelorussia, Ukraine, and Yugoslavia.[19]

Government inducement in the form of tax incentives as well as public financing was used to overcome industry's hesitancy to invest in penicillin facilities during the early development stages of World War II. This was a period of trial and error in production methods, and production units in some cases became obsolete before they were installed. When submerged aeration was developed, earlier wartime installations of flask-type equipment became obsolete and the use of huge fermenters was adopted by all manufacturers remaining in the industry. If the anticipated chemical synthesis of penicillin had become practical, another round of plant replacement would have occurred.

In authorizing accelerated tax amortization, the Government recognized that if the chemical synthesis research program was successful and this process became practical, another round of plant replacement would have occurred.

When the Korean emergency arose, some antibiotics producers already had commenced plant expansions. These expansions were completed and others were undertaken with the aid of certificates of neces-

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15 This total does not include funds spent for research by Federal agencies.

16 James Phinney Baxter 3d, Scientists Against Time, Little, Brown & Co., Boston, 1950, p. 351.

17 UNRRA: Report of the Director General to the Council, Summary of Operations, November 9, 1943, to December 31, 1947, Washington, 1948, p. 283 ff.

18 George Woodbridge, The History of the United Nations Relief and Rehabilitation Administration, vol. I, Columbia University Press, N. Y., 1950, p. 438.

19 UNRRA: Report of the Director General to the Council, Summary of Operations, November 9, 1943, to December 31, 1947, Washington, 1948, p. 190; George Woodbridge, The History of the United Nations Relief and Rehabilitation Administration, vol. I, Columbia University Press, N. Y., 1950, p. 439.

sity and authorizations for rapid depreciation writeoffs similar to those of World War II. Thus, the industry responded rapidly by expansion with private funds invested under favorable conditions, and public funds were not needed for plant construction.

A further dissimilarity between the World War II program and the Korean program is found in the portion of the expanded facilities on which the companies were authorized to take accelerated depreciation. During World War II, most of the facilities were regarded as having little salvage value. However, wartime capacity to produce continued to be needed and expanded to meet civilian demand. With this experience as a background, the Korean program was carried on under the assumption that there would be a substantial postemergency demand for authorized production facilities. In 1950–53, therefore, most of the companies were granted about 60-percent writeoffs; that is, they were allowed to take rapid depreciation on only about 60 percent of the total cost of added production facilities.

The steps by which this was done were as follows: After determining national defense needs, the Government established a procedure by which companies had to apply for certificates of necessity in order to obtain scarce materials for plant construction. Penicillin was established as a miltiary item both in World War II and during the Korean action. When the Government reviewed the applications for certificates of necessity, it also determined what percentage of the proposed construction was "defense related" and what percentage would have postemergency value. The percentage declared to be defense related was allowed for rapid (5 years) amortization for tax purposes.

Antibiotics accounted for 0.2 percent of the total authorized defense plant expansion in World War II, and 0.3 percent of the authorized expansion during the Korean war.

National Capacity for Production in Emergency

The production capacity for penicillin authorized by the War Production Board during World War II was 300 billion units per month, or 3,600 billion units per year. It was assumed that this volume of penicillin would be greatly in excess of normal peacetime requirements, since toward the end of the war (July 1944) 88 percent of the penicillin output in the United States was going to the Armed Forces.[20] In fact, however, this did not prove to be true, for the industry continued to expand by the expenditure of private funds from 1946 onward.

[20] Memorandum from Drugs and Penicillin Facilities Unit, War Production Board, to Tax Amortization Branch, War Production Board, dated July 8, 1944, records of the War Production Board, NA, RG 179, Washington.

By the time of the Korean war antibiotics had become a peacetime requirement and the war situation again made it necessary to expand production if civilian consumption was not to be curtailed. The goal of 600,000 billion units of annual output was met and the program was closed in 1955.

The present annual capacity of antibiotics manufacturers far exceeds the 1955 goal, and exceeds also the total output of antibiotics in any year. A survey conducted by the Department of Commerce in the early part of 1957 [21] discloses that maximum annual penicillin capacity was nearly 804,000 billion units, or 34 percent above the capacity established in 1955. Table 5 relates maximum capacity for output of leading antibiotics to actual production, and shows that industry is prepared to provide for emergency needs. The 1956 output ranged between 37.9 and 70.5 percent of year-end capacity.

TABLE 5.—*Antibiotics production capacity and output: 1956*

[In billion units (BU) and metric tons (T)]

Antibiotics	Maximum annual capacity [1]	Actual production [2]	Percent of capacity
Penicillin	803,900 BU	557,528 BU	69.4
Bacitracin	956 BU	534 BU	55.9
Streptomycin and dihydrostreptomycin	412.3 T	290.8 T	70.5
Neomycin	16.2 T	7.6 T	46.9
Novobiocin	23.2 T	8.8 T	37.9
Tetracycline	205.0 T	99.8 T	48.7
Others [3]	839.9 T	499.1 T	59.4

[1] Source: Department of Commerce, Business and Defense Services Administration Survey, BDSA Form 355, "Producer's Report on Antibiotics Capacity," dated Feb. 15, 1957, Bureau of the Budget No. 41-5701.
[2] FTC data request, 1957.
[3] Antibiotics made by 1 company only.

This table indicates that the industry had substantial percentages of capacity over production of antibiotics in 1956 with which to meet an emergency increase in demand at least 30 to 60 percent greater than the output for all uses in 1956. These figures, however, should not be taken to constitute an absolute limit on the production of any specific antibiotic in an emergency since there is considerable flexibility in the utilization of some of the production facilities. As noted at p. 118, fermentation equipment is "amazingly standard. Therefore, it is generally possible to shift such equipment from the manufacture of one antibiotic to the production of a different antibiotic.

Antibiotics are among the essential materials stockpiled for use in case of an emergency. Purchases of antibiotics by the Armed Forces Medical Procurement Agency for both military use and for civil defense stocks totaled nearly $8.5 million in fiscal year 1955 and nearly

[21] Department of Commerce, Business and Defense Services Administration Survey, BDSA Form 355, "Producer's Report on Antibiotics Capacity," dated February 15, 1957, Bureau of the Budget No. 51-5701.

$7 million in fiscal year 1956.[22] Since these figures do not include either local purchases by military units or purchases for veterans' hospitals and other Government medical centers, the expenditure by the Government for antibiotics was actually considerably larger. Government spending is not, however, a large part of total spending for antibiotics.

In addition to Government stocks, inventories of antibiotics are normally maintained by manufacturers. Company responses to the Commerce Survey mentioned above indicate that the manufacturers' inventories were running at about 33 percent of output in 1956.

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[22] Special report to the Federal Trade Commission by the Armed Forces Medical Procurement Agency, 1957.

CHAPTER III

Antibiotics Production and Manufacturers

It is the purpose of this chapter to show the output of the different antibiotics substances at the producer's level and to relate this production to the mannfacturers indicating their market shares and related economic problems. While the manufacture of antibiotics is referred to as an industry in this report, it is, in fact, a part of the larger pharmaceutical industry, and, in all cases, each individual producer of antibiotics is also a producer of a wide range of other products. Accordingly, it should be recognized at the outset that data on the antibiotics segment of the pharmaceutical industry, or of a firm's business, are not readily available on a separate basis.

In the development of the antibiotics industry, the work of production has been undertaken in the main by old well-known chemical or pharmaceutical houses which had experience either in fermentation technology, manufacture of medicinal chemicals, or production of prescription medicines. The operations of different producing companies present varying degrees of integration from the production of raw materials to the marketing of the finished product. In this chapter, the principal emphasis is placed upon the production level.

Antibiotics Production and Marketing Levels

The four levels of operation discernible in the production and marketing of antibiotics are as follows:

1. *Production of chemical and other raw materials*

A number of the antibiotics manufacturers produce some of their chemical raw material requirements, and others produce none of their raw materials.

2. *Manufacture of bulk antibiotics*

There were 12 manufacturers in 1956, of which 2 were dominant in terms of volume output of antibiotics.

3. *Processing and packaging into dosage or other finished forms*

All of the 12 manufacturers engage to a greater or lesser extent in this level of operation. Outside packagers purchase some types of antibiotics in bulk from the industry and compete with the manufacturers in selling antibiotics products. The manufacturers also purchase some types of bulk antibiotics from each other.

4. *Marketing*

This level is engaged in by the 12 manufacturers in differing intensity in each of the four principal segments of the market:

(*a*) Doctor's approval.
(*b*) Pharmaceutical and cosmetics manufacturers.
(*c*) Other antibiotics manufacturers and wholesalers.
(*d*) New markets in agriculture.

At the first level (production of raw materials for antibiotics manufacture), some of the antibiotics manufacturers produce some of their chemical raw material requirements. The members of the industry which manufacture chemical input requirements may enjoy a competitive cost advantage within the group. The list of chemicals used during the production process is extensive and varies substantially between antibiotics.

At the bulk manufacturing level, there is specialization in certain products, particularly some of the broad spectrums, from company to company. Additional comments about the characteristics of this level of the industry will be found later in this chapter.

At the processing level, it has been the general policy among antibiotics producers to sell part of their production in bulk to outside packagers who compete with the manufacturers in the marketing of medicinal products containing antibiotics. The turnover rate among these packagers, however, appears to be relatively high. In 1956, 45 nonmanufacturing companies advertised medicinal forms of antibiotics in the Drug Topics *Red Book*[1] as compared with 27 in 1950. The number of nonmanufacturing packagers listed in the Red Book for the years 1950 to 1956 is as follows:

Year:	*Number of nonmanufacturing packagers of medicinal antibiotics*
1950	27
1951	26
1952	29
1953	33
1954	30
1955	37
1956	45

While the total number increased from 27 to 45 during the 7 years, the companies making up the total changed rapidly. Seventeen of the 27 companies advertising in 1950 had discontinued publishing prices for medicinal forms by 1956. Thirty-five of the 45 companies included in the 1956 listing had entered the field after 1950. The rapid turnover indicates that although competition is particularly keen, the packaging business is relatively easy to enter.

Antibiotics manufacturers who supply bulk substances to formulators of industrial and agricultural products ordinarily produce no

[1] Topics Publishing Co., Inc., New York, 1957 and 1951 editions.

directly competitive industrial or agricultural product themselves. When an antibiotics substance is sold by its manufacturer for other than medicinal use, it may not be identified with the company's ethical [prescription] drug operations.

At the marketing level, the most important segment of the antibiotics market as a whole is the doctor loyalty market because this is the market in which ethical drug houses necessarily operate. This market is considered rather inelastic with respect to price. The consumption of medicinal antibiotics is controlled fundamentally by the incidence of infections for which they offer effective treatment and by prevailing medical practice. Each antibiotic competes primarily with other antibiotics. The physician selects the one which he regards as most effective in treating the illnesses rather than on the basis of price. The patient exercises no effective choice.

Two factors which have characterized the industry during its 14-year growth (1943–56) are specialization and innovation protected by patents and trademarks. When a company through its research efforts can find, patent, and market a new and popular antibiotic, it has secured a distinct advantage for a time. All the advantages of specialization are automatic because of patent and trademark controls over manufacture and sale of the product. Production and marketing facilities can be pinpointed.

National Output of Antibiotics, 1948-56

Antibiotics are produced primarily for medicinal purposes, but animal feed supplements and other minor uses have grown in importance since 1950. The total national output of the leading products for the years 1948 and 1956 is shown in table 6.

TABLE 6.—*Output of leading antibiotics and percent to total output: 1948 and 1956*

Antibiotic	1948		1956	
	Number of pounds [1]	Percent of total	Number of pounds [1]	Percent of total
Penicillins	155, 873	64. 9	1, 059, 704	34. 4
Streptomycin	80, 737	33. 6	148, 999	4. 8
Dihydrostreptomycin	2, 989	1. 2	492, 173	16. 0
Chlortetracycline	661	. 3	560, 663	18. 2
Oxytetracycline			324, 614	10. 5
Tetracycline			220, 074	7. 1
Chloramphenicol	46	(2)	85, 408	2. 8
Erythromycin	0		70, 913	2. 3
All others	26	(2)	118, 825	3. 9
Total	240, 332	100. 0	3, 081, 373	100. 0

[1] Penicillin has been measured in international units of potency. Louis S. Goodman and Alfred Gilman, The Pharmacological Basis of Therapeutics, The Macmillan Co., New York, 1956, p. 1239. In this study conversion to pounds is done on the basis of published potency ratios. (See appendix III.) These ratios vary from 1 penicillin salt to another, and do not always conform to the ratios used by the Tariff Commission in its annual reports.

[2] Less than 0.1 percent.

Source: FTC data requests, 1956 and 1957.

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By 1956 animal feeds represented over 27 percent of total antibiotics output. Table 7 lists the kinds of antibiotics used in animal feed supplements and shows the percent of production of each to total feed supplement output.

TABLE 7.—*Antibiotics produced for animal feed supplement as a percentage of total output for feed supplements: 1956*

Name of antibiotic	Number of pounds manufactured	Percent of total output for feed supplements
Penicillin procaine	173,455	20.5
Streptomycin	8,250	.9
Bacitracin	21,104	2.5
Chlortetracycline	465,197	54.9
Oxytetracycline	179,190	21.2
Neomycin	29	(1)
Total	847,225	100.0

1 Less than 0.1 percent.

Source: FTC data request, 1957.

Chart 1 lists all of the antibiotic substances that have been produced commercially together with the periods of production from 1948 to 1956.

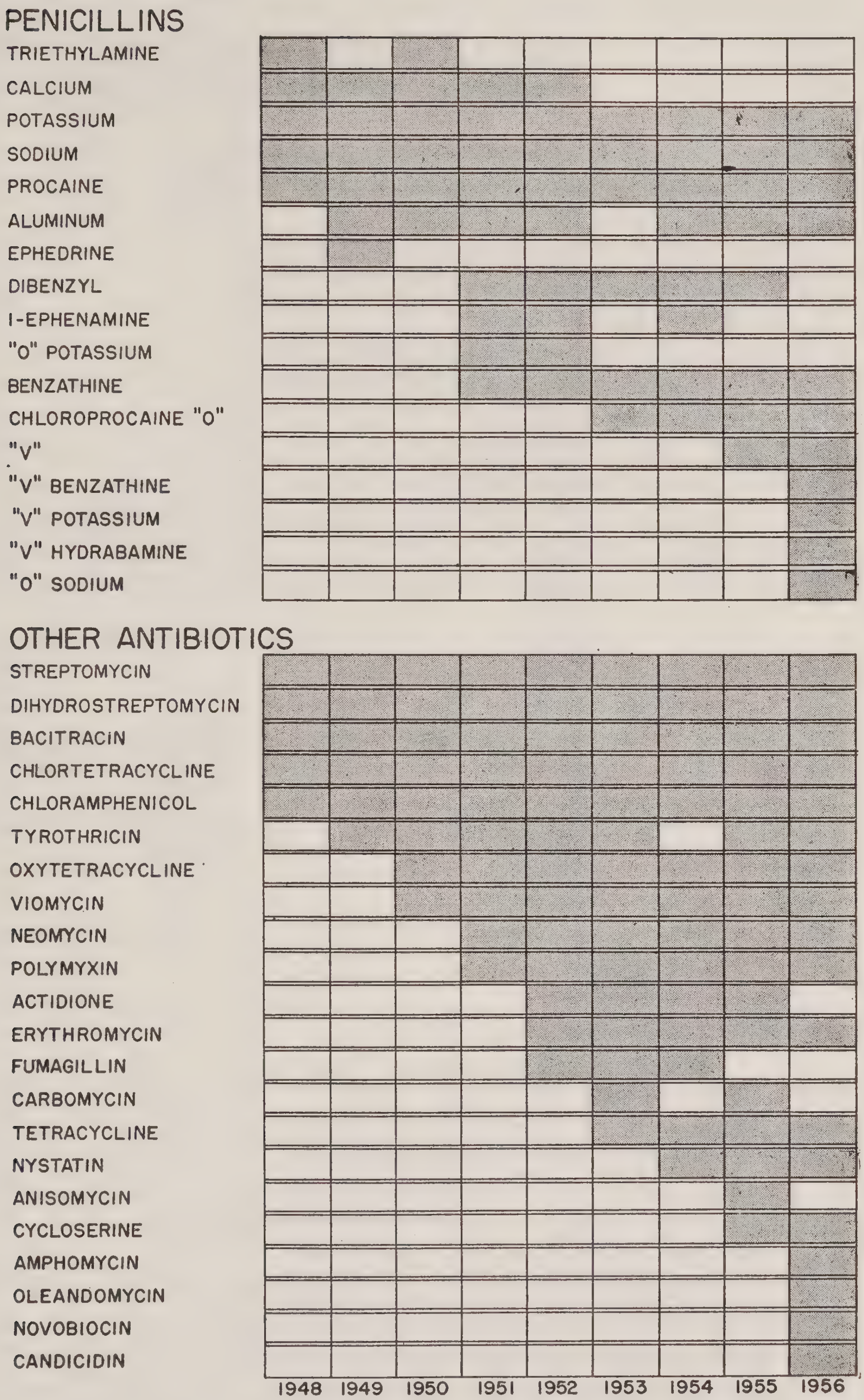
In chart 2, total output of major antibiotics by grade is shown for the year 1956 and the proportion of each which was manufactured for animal feed supplements. On a quantity basis the most important antibiotics are penicillin and the streptomycins, but chlortetracycline outranks all other antibiotics in the feed supplement field.

Chart 3 shows the growth of total volume output from 1948 through 1956. While by far the greater part of the production is of medicinal grade, the rising importance of feed supplements as a part of total output is also shown. Production for agricultural uses, such as in crop spraying or in food preservation, appeared for the first time in 1956.

Penicillin, as shown in table 6, represented nearly 65 percent of total output in 1948; its share of total output in 1956 was 34.4 percent, but it was still manufactured in almost twice the volume of the next ranking volume item, chlortetracycline. Penicillin output increased from 92,947 billion units (BU) in 1948, for 5 different kinds of penicillin salts, to 557,528 BU in 1956 for 11 penicillin salts. In 1948 procaine penicillin accounted for 36,140 BU of production (38.9 percent of total penicillin output) and in 1956, for 353,781 BU (63.5 percent of total penicillin output). Procaine penicillin was the only penicillin used in animal feed supplements in 1956.

Chart 4 shows total output of penicillins in billions of units for the years 1948 to 1956, inclusive, and also the relative importance of procaine, potassium and penicillin V production to total penicillin output. Penicillin V, significant as a new oral penicillin product, was first marketed in 1955.

Years in which each Antibiotic was Produced 1948 - 1956



SOURCE: FTC DATA REQUESTS, 1956 AND 1957.

CHART 1.

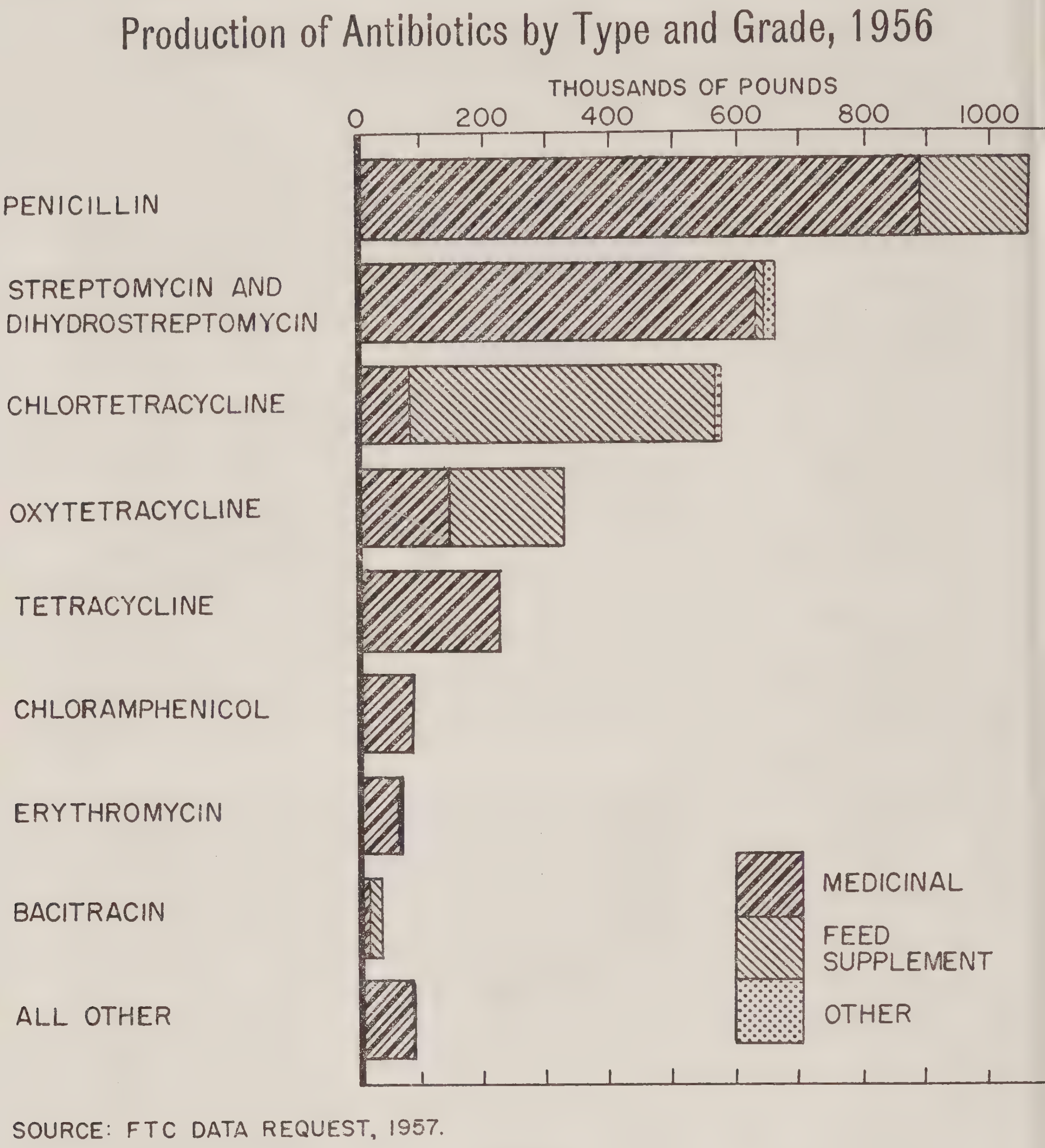


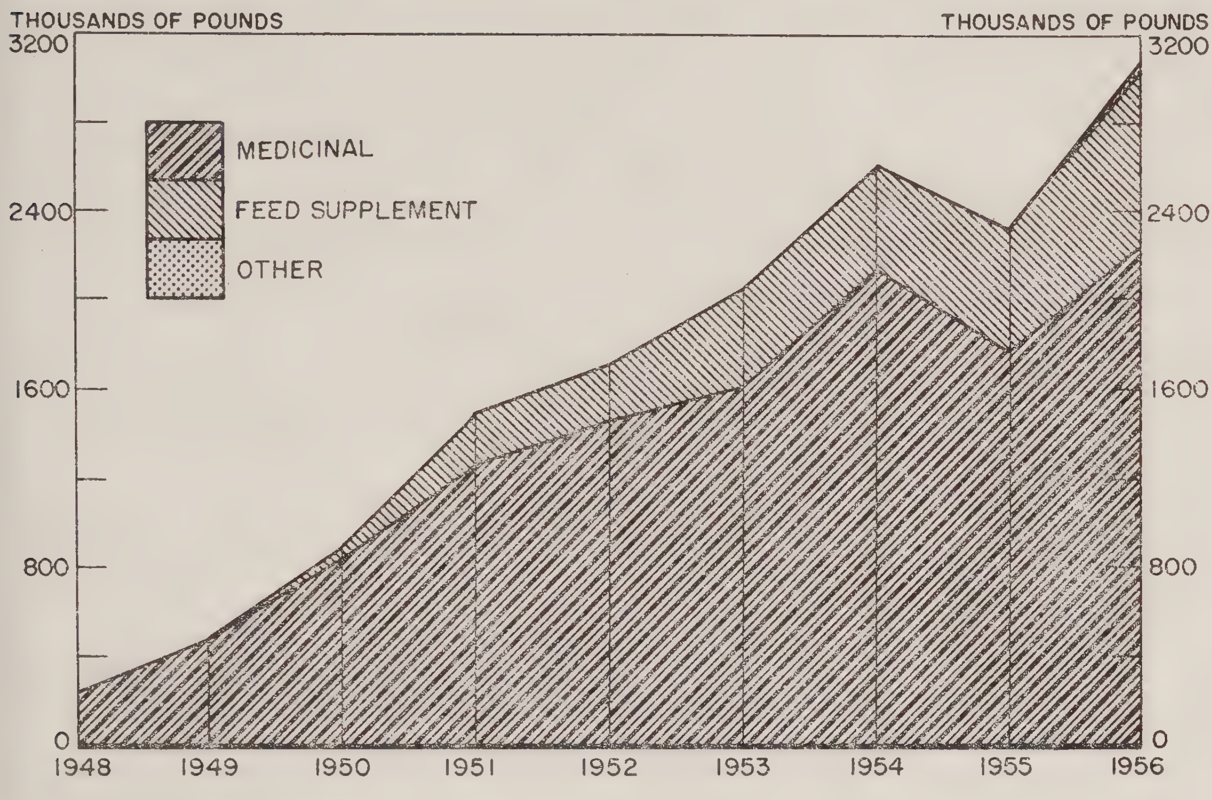
CHART 2.

Streptomycin, the second major type of antibiotic to be developed, was first manufactured at the close of World War II (1946). From an output of over 80,000 pounds in 1948, production declined to 38,686 pounds in 1951. But by 1955 production had reached 154,415 pounds. Streptomycin was first used in animal feed supplements in 1955, but accounted for only 1,067 pounds.

Production of dihydrostreptomycin increased rapidly from 2,989 pounds in 1948 reaching a peak in 1956 when 492,173 pounds were manufactured. None of this substance is used in animal feeds.

Chloramphenicol was first reported in 1948, and reached its highest output of 85,408 pounds in 1956. It is not produced as an animal feed supplement. This is one of the "broad spectrum" antibiotics, so called because of the wide range of micro-organisms which it will destroy or whose growth it will inhibit.

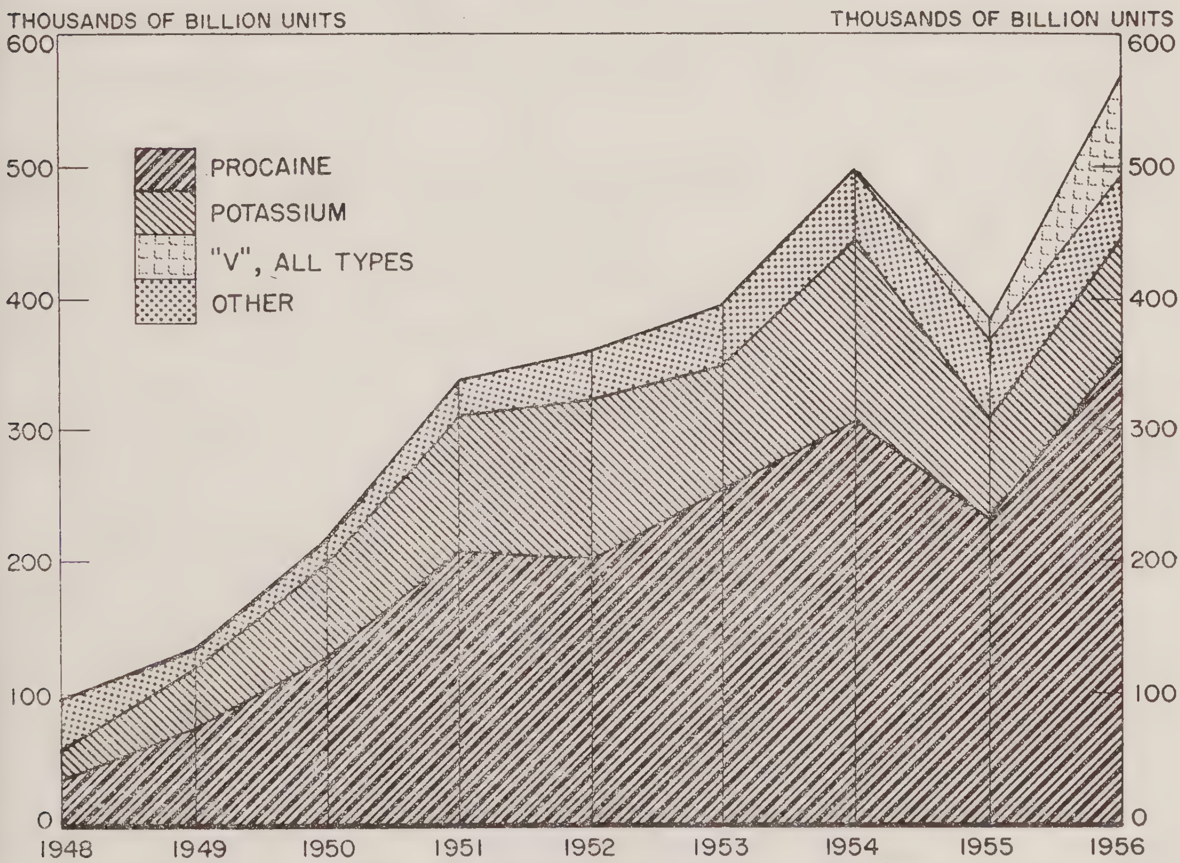
Production of Antibiotics by Grade, 1948-1956



SOURCE: FTC DATA REQUESTS, 1956 AND 1957.

CHART 3.

Production of Penicillin, 1948-1956



SOURCE: FTC DATA REQUESTS, 1956 AND 1957.

CHART 4.

Chlortetracycline, from an output of 661 pounds in 1948, reached a peak of 560,663, pounds in 1956. Of this output 465,197 pounds, or 83 percent, were for animal feed supplements; 8,962 pounds for crop spraying and food preservation and the balance of 86,504 pounds for medicinals. This antibiotic is called a "broad spectrum."

Oxytetracycline output has increased steadily from 37,948 pounds in 1950 to 324,614 pounds in 1956, over half being used for animal feeds. This is the third of the "broad spectrum" antibiotics.

Tetracycline was first manufactured in 1953, and by 1956, 220,074 pounds were produced. Output was highest in 1954 (270,235 pounds). Tetracycline has not been used for animal feeds except for a small amount in 1955. This substance is the fourth "broad spectrum" antibiotic.

Erythromycin was first manufactured in 1952. In 1956, the total output was 70,913 pounds. No animal feed supplements are manufactured from this antibiotic.

Bacitracin was first produced in 1948 and totaled only 26 pounds. By 1956, 23,622 pounds were produced, nearly 90 percent being for animal feed supplement.

Novobiocin was first produced in 1956 with the production totaling 19,410 pounds. Novobiocin has not been used for animal feeds.

Neomycin was first manufactured in 1951. The output in 1956 totaled 16,925 pounds, all except 29 pounds being for medicinal products.

Other antibiotics, viomycin, polymyxin, carbomycin, amphomycin, anisomycin, tyrothricin, nystatin, oleandomycin, and candicidin are relatively minor, but reference will be made to them in special connections from time to time.

Increases in production have paralleled growing domestic and export demands for antibiotics in recent years. Although production from 1943 through 1948 was significant, complete records have not been kept by the companies for the early wartime years. Therefore, the ensuing discussion is based on statistics for the years 1948 through 1956.

In terms of total volume, production of antibiotics in the United States increased from 240,332 pounds in 1948 to 3,081,373 pounds in 1956—nearly a thirteenfold increase in 9 years.

The production of new salts of penicillin, following the Government's wartime program, proceeded (as shown in table 8) at the same time that other new antibiotics substances were being developed and produced.

National output of each distinctive type of antibiotic for the years 1948 through 1956 is tabulated in table 9. In this table, all penicillins have been grouped into one total of billions of potency "units" (BU) and equivalent pounds avoirdupois for each year. Tables 8 and 9 show the quantity of production of all the antibiotics substances listed on chart 1 appearing on page 69.

TABLE 8.—*National output of penicillin: 1948 to 1956*

Penicillin salts	Grade [1]	1948		1949		1950		1951		1952		1953		1954		1955		1956	
		BU*	Number of manufacturers	BU	Number of manufacturers	BU	Number of manufacturers	BU	Number of manufacturers	BU	Number of manufacturers	BU	Number of manufacturers	BU	Number of manufacturers	BU	Number of manufacturers	BU	Number of manufacturers
Triethylamine	M	571	1	------	------	170	1	------	------	------	------	------	------	------	------	------	------	------	------
Calcium	M	3, 139	9	52	3	10	1	5	1	5	1	------	------	------	------	------	------	------	------
Potassium	M	22, 740	6	46, 964	13	70, 239	13	101, 474	12	122, 147	13	94, 210	11	140, 782	11	76, 920	9	89, 192	7
	FS	------	------	------	------	------	------	------	------	60	1	------	------	------	------	41	1	------	------
Sodium	M	30, 357	12	12, 492	9	18, 670	7	20, 708	8	12, 225	8	20, 209	6	29, 013	6	28, 588	5	20, 644	3
Procaine	M	36, 140	14	75, 335	14	127, 584	13	193, 609	13	189, 104	13	241, 276	11	287, 167	10	195, 019	9	274, 512	7
	FS	------	------	------	------	1, 899	1	11, 916	1	11, 374	4	16, 312	6	21, 118	5	36, 583	7	79, 269	6
Aluminum	M	------	------	151	1	230	1	74	1	756	1	------	------	30	1	6	1	7	1
Ephedrine	M	------	------	33	1	------	------	------	------	------	------	------	------	------	------	------	------	------	------
Dibenzylethylenediamine	FS	------	------	------	------	------	------	1, 077	1	3, 528	1	2, 411	1	606	1	751	1	------	------
1-Ephenamine	M	------	------	------	------	------	------	2, 880	1	367	1	------	------	825	1	------	------	------	------
"O" potassium	M	------	------	------	------	------	------	91	1	1, 027	1	------	------	------	------	------	------	------	------
Benzathine	M	------	------	------	------	------	------	577	1	19, 078	3	22, 120	4	22, 994	2	26, 910	2	22, 564	2
	FS	------	------	------	------	------	------	------	------	------	------	------	------	------	------	104	1	------	------
"O" chloroprocaine	M	------	------	------	------	------	------	------	------	------	------	326	1	77	1	152	1	143	1
"V"	M	------	------	------	------	------	------	------	------	------	------	------	------	------	------	17, 181	2	61, 081	1
"V" hydrabamine	M	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	2, 836	1
"V" potassium	M	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	1, 380	1
"V" benzathine	M	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	5, 855	1
"O" sodium	M	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	45	1
Total medicinal grade	------	92, 947	15	135, 027	15	216, 903	13	319, 418	13	344, 709	13	378, 141	12	480, 888	11	344, 776	9	478, 259	8
Total animal feed supplement	------	------	------	------	------	1, 899	1	12, 993	2	14, 962	7	18, 723	6	21, 724	5	37, 479	7	79, 269	6
Total penicillin	------	92, 947	------	135, 027	------	218, 802	------	332, 411	------	359, 671	------	396, 864	------	502, 612	------	382, 255	------	557, 528	------

*Billions of units.
[1] Medicinal grade "M" and animal feed supplement "FS" shown separately.

Source: FTC data requests, 1956, 1957.

TABLE 9.—*National output of antibiotics: 1948 to 1956*

Antibiotic generic name	Grade [1]	Unit [2]	1948			1949			1950			1951		
			Units	Pounds	Number of manufacturers	Units	Pounds	Number of manufacturers	Units	Pounds	Number of manufacturers	Units	Pounds	Number of manufacturers
Penicillin	M	BU	92, 947	155, 873	15	135, 027	247, 053	15	216, 903	402, 179	13	319, 418	599, 361	13
	FS	BU							1, 899	4, 155	1	12, 993	28, 039	2
Streptomycin	M	KG	36, 662	80, 737	8	24, 636	54, 312	8	20, 710	45, 657	7	17, 548	38, 686	7
	FS	KG												
	AG	KG												
Dihydrostreptomycin	M	KG	1, 356	2, 989	2	63, 052	139, 004	7	71, 556	157, 752	7	142, 981	315, 216	7
Bacitracin	M	MU	600	26	1	46, 800	2, 071	1	71, 189	3, 150	1	74, 867	3, 313	2
	FS	MU										1, 115, 624	49, 364	1
Chlortetracycline	M	KG	300	661	1	12, 935	28, 517	1	50, 459	111, 242	1	70, 563	155, 563	1
	FS	KG							14, 353	31, 643	1	42, 446	93, 576	1
	AG	KG												
Chloramphenicol	M	KG	21	46	1	5, 719	12, 608	2	32, 464	71, 570	2	41, 627	91, 771	2
Tyrothricin	M	KG				34	75	1	25	55	1	20	44	1
Oxytetracycline	M	KG							16, 622	36, 645	1	25, 426	56, 054	1
	FS	KG							591	1, 303	1	29, 746	65, 578	1
Viomycin	M	KG							50	110	1	56	123	1
Neomycin and salts	M	KG										678	1, 495	2
	FS	KG												
Polymyxin	M	BU										2	1	1
Actidione	M	KG												
Erythromycin	M	KG												
Fumagillin	M	KG												
Carbomycin	M	KG												
Tetracycline	M	KG												
	FS	KG												
Nystatin	M	BU												
Anisomycin	M	KG												
Cycloserine	M	KG												
Amphomycin	M	KG												
Novobiocin	M	KG												
Oleandomycin	M	KG												
Candicidin	M	KG												
Total	M			240, 332	16		483, 640	17		828, 360	17		1, 261, 627	17
Total	FS									37, 101	3		236, 557	4
Total	AG													
Grand total, M, FS, AG				240, 332			483, 640			865, 461			1, 498, 184	

[1] Medicinal grade "M," animal feed supplement "FS," agricultural use "AG" shown separately.
[2] Units of production as reported by manufacturers. (Conversion to pounds, shown on the table, were based on the ratios listed in appendix III.

Source: FTC data requests 1956, 1957.

Antibiotic generic name	Grade[1]	Unit [2]	1952			1953			1954			1955			1956		
			Units	Pounds	Number of manufacturers	Units	Pounds	Number of manufacturers	Units	Pounds	Number of manufacturers	Units	Pounds	Number of manufacturers	Units	Pounds	Number of manufacturers
Penicillin	M	BU	344, 709	638, 138	13	378, 141	726, 687	12	480, 888	906, 250	11	344, 776	643, 301	9	478, 259	886, 249	8
	FS	BU	14, 962	31, 259	7	18, 723	40, 094	6	21, 724	47, 316	5	37, 479	81, 666	7	79, 269	173, 455	6
Streptomycin	M	KG	22, 528	49, 665	7	56, 761	125, 135	6	64, 068	141, 244	7	70, 042	154, 415	6	58, 865	129, 774	5
	FS	KG										484	1, 067	1	3, 742	8, 250	1
	AG	KG													4, 978	10, 975	2
Dihydrostreptomycin	M	KG	152, 855	336, 984	6	138, 342	304, 989	7	202, 217	445, 808	7	167, 490	369, 248	6	223, 248	492, 173	5
Bacitracin	M	MU	103, 459	4, 578	3	129, 941	5, 750	3	151, 801	6, 717	3	89, 411	3, 956	4	56, 918	2, 518	4
	FS	MU	242, 802	10, 743	2	28, 052	1, 241	2	66, 456	2, 941	2	138, 342	6, 121	2	476, 942	21, 104	2
Chlortetracycline	M	KG	68, 932	151, 967	1	89, 338	196, 955	1	26, 577	58, 592	1	25, 200	55, 556	1	39, 238	86, 504	1
	FS	KG	72, 676	160, 222	1	127, 888	281, 942	1	128, 950	284, 283		127, 546	281, 188	1	211, 012	465, 197	1
	AG	KG													4, 065	8, 962	1
Chloramphenicol	M	KG	61, 996	136, 676	2	2, 219	4, 892	2	6, 419	14, 151	1	24, 206	53, 365	1	38, 741	85, 408	1
Tyrothricin	M	KG	401	884	1	72	159	1				281	619	1	496	1, 093	1
Oxytetracycline	M	KG	56, 140	123, 766	1	67, 124	147, 982	1	84, 487	186, 260	1	69, 119	152, 380	1	65, 964	145, 424	1
	FS	KG	24, 156	53, 254	1	48, 366	106, 628	1	72, 753	160, 391	1	80, 345	177, 129	1	81, 280	179, 190	1
Viomycin	M	KG	129	284	1	375	827	1	912	2, 011	1	1, 306	2, 879	1	1, 420	3, 131	1
Neomycin and salts	M	KG	3, 702	8, 161	2	5, 943	13, 102	3	11, 225	24, 747	5	12, 574	27, 721	5	7, 664	16, 896	6
	FS	KG													13	29	1
Polymyxin	M	BU	946	336	1	637	226	1	1, 145	407	1	1, 124	400	1	1, 324	471	1
Actidione	M	KG	41	90	1	205	452	1	432	952	1	297	655	1			
Erythromycin	M	KG	1, 125	2, 480	2	17, 853	39, 359	3	29, 058	64, 061	3	24, 108	53, 148	2	32, 166	70, 913	2
Fumagillin	M	KG	161	355	1	77	170	1	66	146	1						
Carbomycin	M	KG				990	2, 183	1				16	35	1			
Tetracycline	M	KG				18, 032	39, 753	2	122, 578	270, 235	3	116, 604	257, 065	3	99, 825	220, 074	3
	FS	KG										372	820	1			
Nystatin	M	BU							5, 370	3, 399	1	24, 685	15, 623	1	34, 895	22, 085	1
Anisomycin	M	KG										11	24	1			
Cycloserine	M	KG										289	637	1	6, 440	14, 198	2
Amphomycin	M	KG													33	73	1
Novobiocin	M	KG													8, 804	19, 410	2
Oleandomycin	M	KG													8, 081	17, 815	1
Candicidin	M	KG													1	2	1
Total	M			1, 454, 364	17		1, 608, 621	15		2, 124, 980	12		1, 791, 027	12		2, 214, 211	12
Total	FS			255, 478	10		429, 905	9		494, 931	8		547, 991	9		847, 225	9
Total	AG															19, 937	2
Grand total, M, FS, AG				1, 709, 842			2, 038, 526			2, 619, 911			2, 339, 018			3, 081, 373	

[1] Medicinal grade "M," animal feed supplement "FS," agricultural use "AG" shown separately.
[2] Units of production as reported by manufacturers. (Conversion to pounds, shown on the table, were based on the ratios listed in appendix III.

Source: FTC data requests 1956, 1957.

The quantity of output is reported by manufacturers in different units for different products. In table 9 these units are shown together with equivalents in pounds.[2]

Referring to table 8 on the production of the different salts of penicillin, it should be noted that 5 kinds were produced commercially in 1948 and 11 kinds in 1956. Only 3 of the 11 kinds of penicillin produced in 1956 were reported in every year shown. Since January 1, 1949, a total of 12 new penicillin salts have been brought into production, making a total of 17 on which output was reported in one or more years. Two of the five for which output was reported in 1948 were not produced in 1956, and four other newer kinds for which some output was reported in one or more later years also showed no output in 1956. Thus, for 6 of the 17 kinds for which production was reported in one or more years of the period, no output was shown in 1956. The net result is that the number of kinds of penicillin salts produced varied from year to year, and ranged from 5 in 1948 to 11 in 1956.

Tables 8 and 9 list 17 penicillins and 22 other antibiotic substances, making a total of 39 antibiotic substances, each of which has been produced in at least small quantities in one or more years during the period, 1948 through 1956. Chart 1 shows for the same period the years in which the 17 penicillins and 22 other antibiotic substances have been manufactured. In 1956, 4 new penicillin specialties were manufactured, as well as 4 other new basic substances, making a total of 8 new products reported in that year. This is the largest number of new products to be introduced in a single year.

Total Value of Antibiotics at Producer's Level

The preceding presentations of production data on the different kinds of antibiotics have been entirely on a quantity basis. Further appreciation of the relative importance of these different substances produced may be gained by considering the dollar values of the products marketed from the manufacturers' own production.[3] Charts 5,

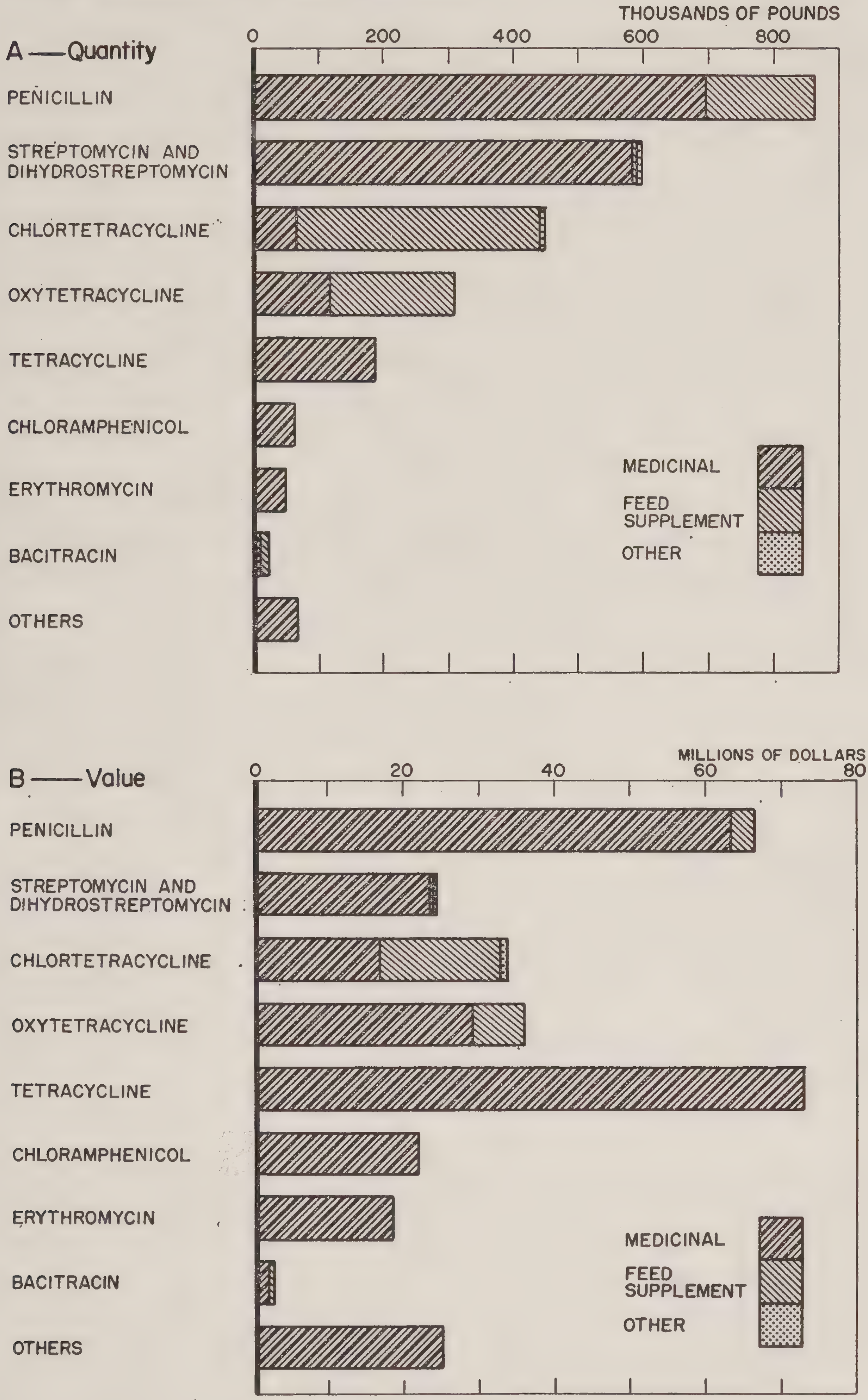
[2] The conversion rates used are listed in Appendix III.

[3] "Manufacturers' sales from own production" (as reported on schedule I of the FTC Survey of 1956 and schedule IV of the FTC Survey of 1957 and as reported annually by the manufacturers to the Tariff Commission) excludes sales of purchased antibiotics. "Manufacturers' total net sales" (as reported on Accounting schedules I and II of the FTC Data Requests of 1957, and as discussed in ch. VII) includes sales of purchased antibiotics. A comparison of these series follows:

Year	Manufacturers' sales from own production (millions)	Manufacturers' total net sales (millions)	Own production as percent of total
1950	$204.6	$249.2	82.1
1951	316.5	344.1	92.0
1952	243.1	289.1	84.1
1953	243.8	270.4	90.2
1954	263.6	287.9	91.6
1955	267.3	304.1	87.9
1956	301.4	337.7	89.3

Sales of Antibiotics by Type and Grade, 1956

From Manufacturers' Own Production



SOURCE: FTC DATA REQUEST, 1957.

CHART 5.

part A, and 5, part B, show the quantity in pounds and value in dollars of leading antibiotics sold by all antibiotics manufacturing companies from their own production in 1956. Penicillin totaled 866,000 pounds; streptomycins, 591,000 pounds; and the four broad spectrums (chlortetracycline, oxytetracycline, tetracycline, and chloramphenicol) 1,001,000 pounds. (Further details are presented in table 10.)

By comparing parts A and B of chart 5, it is evident that there is a wide difference in the dollar values of the different antibiotics. The nine antibiotic substances named in part B account for about 92 percent of the $301,400,000 total for manufacturers' sales from their own production as shown in table 10. The four broad spectrums constitute about 55 percent of the total value.

The quantity and value comparisons in parts A and B of chart 5 and in table 10 indicate that while the penicillins and streptomycins are sold in much greater quantities than the remaining antibiotics listed, they are of relatively lower total value.

It should be pointed out that some of the antibiotics listed in table 10 are sold in several grades; others are prepared only in medicinal grade, while yet others are prepared primarily as feed supplements. Dollar values vary widely among the different grades.

TABLE 10.—*Quantity and value of manufacturers' sales of own production of antibiotics: 1956* [1]

Antibiotic substance [2]	Quantity (pounds)	Value (millions)
Penicillin	866,000	$66.6
Streptomycin and dihydrostreptomycin	591,000	24.2
Chlortetracycline	442,000	33.7
Oxytetracycline	310,000	36.3
Tetracycline	186,000	72.9
Chloramphenicol	63,000	22.1
Erythromycin	49,000	18.2
Bacitracin	24,000	2.3
All others	66,000	25.1
Total	2,597,000	$301.4

[1] Excluding sales of purchased antibiotics.
[2] Includes dosage, bulk, feed supplement, and other forms.

Source: FTC data request, 1957.

Manufacturers' sales of the medicinal grades of the different antibiotic substances are shown in table 11. Medicinal grades total 70.5 percent of the quantity and 90.7 percent of the value of manufacturers' sales of own production.

Animal feed supplements in 1956 accounted for 29.2 percent of the total quantity and for 9.0 percent of the total dollar value. Products sold for other agricultural and industrial uses were negligible by comparison. Table 12 lists the volume and dollar value of feed supplement sales of each substance sold for this purpose. The feed supplement category of sales represent a minor item in 1956, but increasing pro-

TABLE 11.—*Manufacturers' sales of medicinal grade antibiotics: 1956* [1]

Antibiotic substance [2]	Quantity (pounds)	Value
Penicillin "V," all types	56, 833	$14, 437, 180
Penicillin—all other	642, 286	49, 089, 708
Streptomycin and dihydrostreptomycin	577, 679	23, 802, 414
Chlortetracycline	65, 864	17, 048, 929
Oxytetracycline	119, 156	29, 096, 438
Tetracycline	186, 164	72, 902, 971
Chloramphenicol	63, 305	22, 104, 529
Erythromycin	48, 937	18, 220, 130
Bacitracin	4, 266	1, 557, 963
All others	65, 560	25, 051, 855
Total	1, 830, 050	$273, 312, 117

[1] Excluding sales of purchased antibiotics.
[2] Both bulk and dosage forms are included.

Source: FTC data request, 1957.

motional efforts are being made to stimulate agricultural and industrial uses with increases in production and sales as indicated by chart 3 and parts A and B of chart 6.

Tetracycline, the highest value single item, was all sold in medicinal grade in 1956. In 1955 it represented over 26 percent of the total value of sales from manufacturers' own production of all antibiotics, and in 1956, 24 percent. Yet, the total quantity of tetracycline sold in 1956 is only slightly over 7 percent of the total quantity of all antibiotics sold during that year at the manufacturers' level.

TABLE 12.—*Manufacturers' sales of feed supplement grade antibiotics: 1956* [1]

Antibiotic substance	Quantity (pounds)	Value
Penicillin procaine [2]	166, 933	$3, 071, 881
Streptomycin	8, 250	280, 650
Chlortetracycline	371, 205	15, 795, 003
Oxytetracycline	191, 208	7, 154, 220
Bacitracin	19, 681	770, 175
Total	757, 277	$27, 071, 929

[1] Excluding sales of purchased antibiotics and products sold for other agricultural and industrial uses.
[2] A small amount of penicillin benzathine is included in this item.

SOURCE: FTC data request, 1957.

In contrast to tetracycline, the penicillins represent about 33 percent of the total quantities of all antibiotics sold from the manufacturers' own production, but only 22 percent of the total value of all antibiotics at the manufacturers' level. It should be noted in this connection that procaine penicillin, which is produced and sold in quantities much larger than any other salt of penicillin, sells at relatively low prices for both medicinal and animal feed uses. Similarly, sodium and potassium penicillins, which are produced only for medicinal use, sell at relatively low prices, while some of the newer salts introduced during or since

1951 sell at higher prices.[4] As a group, however, the showing of the charts is that the penicillins produce relatively low total revenue.

Oxytetracycline accounted for about 12 percent of the total quantities and about 12 percent of the total value of all antibiotics sold at the manufacturers' level and from the manufacturers' own production in 1956. As shown in tables 11 and 12, more than three-fifths of its output is of feed supplement grade and the balance is for medicinal use.

The proportion sold as feed supplements had an even more important effect upon the dollar value represented by chlortetracycline than it had upon oxytetracycline. In 1956, the total quantity of chlortetracycline was about 17 percent of the total quantity of all antibiotics sold at the manufacturers' level from the manufacturers' own production, and accounted for 11 percent of the total dollar value. However, only 15 percent of chlortetracycline was sold for medicinal purposes, while the balance of about 85 percent was sold for feed supplement and other agricultural uses. Despite the small volume of chlortetracycline of medicinal grade, the dollar value for medicinal sales accounted for more than 50 percent of the total sales of chlortetracycline. Thus, the larger volume of sales for nonmedicinal uses explains the low overall average dollar value per pound of chlortetracycline.

Chloramphenicol has been manufactured only for medicinal purposes. Its dollar value in relation to quantity sold is relatively high as shown in chart 5. The relation of quantity of chloramphenicol to value is similar to that of tetracycline.

Streptomycin and dihydrostreptomycin, which together are sold in larger quantities than other antibiotics except penicillin, represented relatively low dollar values in relation to quantity in striking contrast to all tetracyclines and chloramphenicol. Sales of streptomycin and dihydrostreptomycin from the manufacturers' own production for nonmedicinal uses have been very small and thus had little effect upon the overall dollar value per pound.

The total quantities of all antibiotics sold from the manufacturers' own production, and the total dollar values of these quantities for each of the years from 1948 through 1956 are compared graphically in parts A and B of chart 6.

The quantity of all antibiotics sales in 1956 increased about sixteenfold over 1948 (part A of chart 6). In terms of dollar value, a peak year occurred in 1951 during the Korean war (part B of chart 6). Following that year a decrease in dollar value of sales took place. Although volume increased substantially, the total dollar sales had not regained the 1951 level by 1956, as can be seen from chart 6. Thus, while quantity sold increased about 16 times, the manufacturers' revenue for this quantity only doubled during this period.

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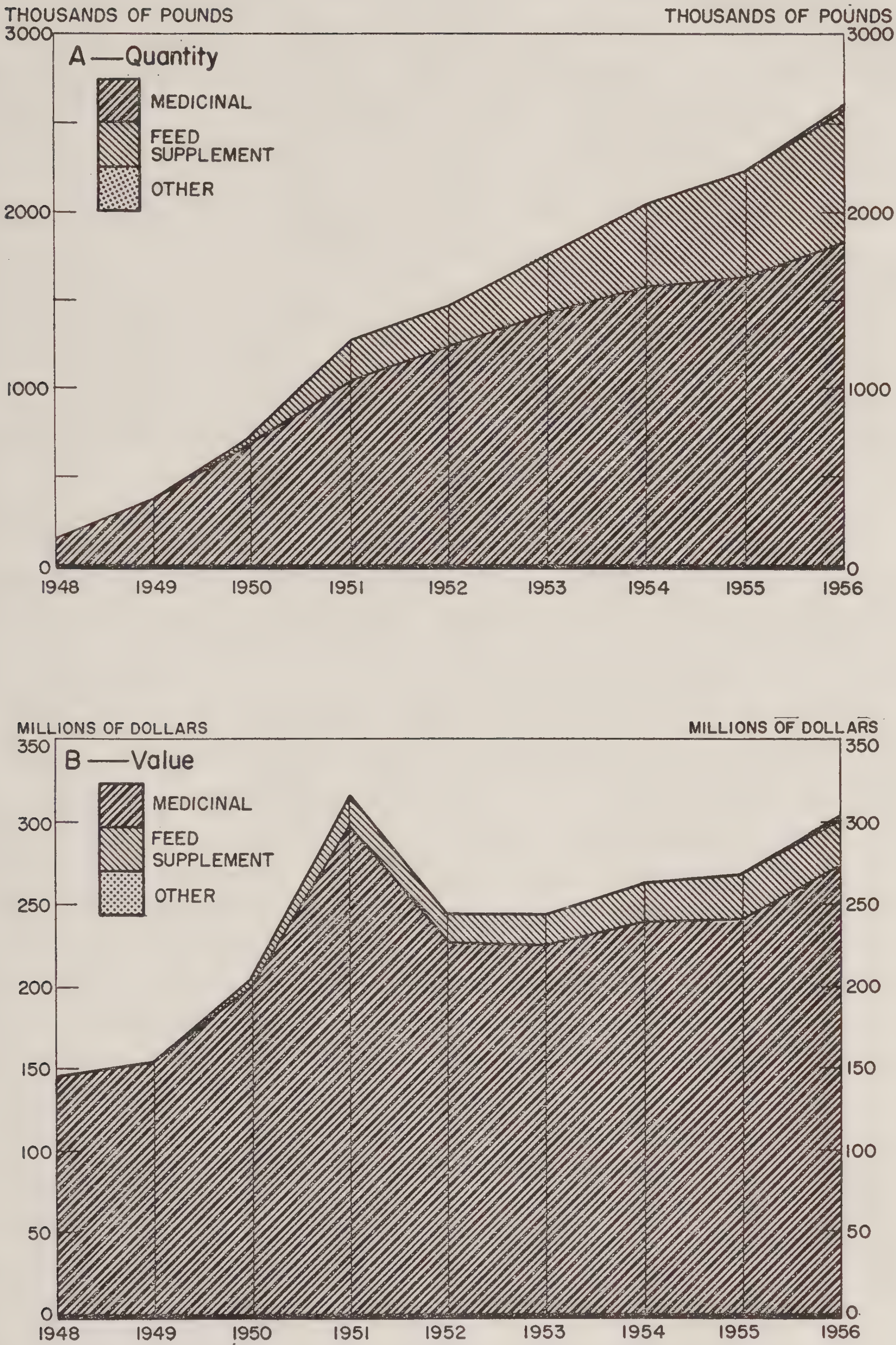
[4] See ch. VI of this report.

Sales of Antibiotics by Grade, 1948–1956

From Manufacturers' Own Production



SOURCE: FTC DATA REQUESTS, 1956 AND 1957.

CHART 6.

Antibiotics Manufacturing Firms

The antibiotics industry includes many of the oldest drug and chemical houses. Such names as Abbott; Lilly; Merck; Parke, Davis; Squibb; Upjohn; and Wyeth have long been well known. The Abbott name, for example, dates from 1888; Lilly was established 12 years earlier. The Merck name in the United States goes back to 1891; but in Darmstadt, Germany, it was first used in the drug business in 1668.[5] Parke, Davis began in 1866; Squibb in 1858; Upjohn in 1884; and Wyeth in 1860. In addition to these old drug houses and some newer ones such as Bristol, Lederle, Penick, and Commercial Solvents, the antibiotics industry has included Pfizer, Monsanto, and Schenley Laboratories, predominantly manufacturers of industrial or fine chemicals. The last two (Monsanto and Schenley) have discontinued antibiotics production. Pfizer, producer of fine chemicals since 1849, and Commercial Solvents entered the ethical drug field after becoming manufacturers of antibiotics.

The industry began during World War II with about 20 companies, and by the end of 1954 only 12 manufacturers remained. This number continued to form the antibiotics industry in 1956. All except one of the present manufacturers of antibiotics began to produce antibiotics during World War II period. Penick, which began the manufacture of antibiotics in 1949, is the exception. Several of the authorized World War II manufacturers discontinued antibiotics manufacture during the ensuing years. Some of them apparently never actually manufactured antibiotics substances on a commercial scale.[6] The 1956 status of these companies, insofar as antibiotics operations are concerned, is shown in table 13.

The nine companies which had dropped out of the manufacturing industry by 1954 were relatively small antibiotics producers, or, in some cases, they may not have produced antibiotics at all.[7]

The first production units used during World War II contained only flask-type equipment which was replaced by large fermentation vats by the large-scale producers toward the end, and following the war. The small producer or pilot plant operator could not compete with large-scale manufacturers.

The following information relative to antibiotics market shares is based on responses to Federal Trade Commission data requests in 1956 and 1957. Among the surviving producers in 1956, approximately half of total antibiotics output was attributable to two companies. In 1955 Pfizer had led with about 35 percent of total volume

[5] Business Week, April 19, 1941, p. 36.

[6] Table 3, p. 54, lists the Government-authorized manufacturers for the World War II period.

[7] See first footnote to table 13.

TABLE 13.—*1956 status of World War II authorized manufacturers of antibiotics* [1]

Manufacturing under same ownership	Manufacturing under new name or ownership	Manufacturing not undertaken or discontinued
Abbott Laboratories.	Heyden Chemical Co. (Antibiotics Division) (now American Cyanamid).	American Home Products (Reichel).
American Cyanamid (Lederle).	E. R. Squibb & Sons (now Olin Mathieson).	Ben Venue Laboratories.
American Home Products (Wyeth).		Cherokee Biological Laboratories.
Commercial Solvents.		Cutter Laboratories.
Eli Lilly & Co.		Emerson & Dettleback.
Parke, Davis.		Hoffmann-LaRoche.
Chas. Pfizer.		Merrell, Wm., & Co. (now Vick Chemical Co.).
The Upjohn Co.		Schenley Distillers.
Cheplin Biological Laboratories (Bristol).[2]		Sterling Drug Co.
Merck & Co.		

[1] The above table lists 9 war-authorized producers which discontinued manufacture. Reichel production facilities were combined with American Home Products' Wyeth operations; Ben Venue Laboratories and Sterling Drug Co. ceased production at the close of World War II; available data do not indicate that Cherokee Biological Laboratories, Wm. Merrell & Co., and Emerson & Dettleback ever produced on a laboratory or commercial scale; Cutter Laboratories last manufactured in 1953 (when production was only 6,385 pounds); Hoffmann-LaRoche last manufactured in 1949 (when total output was only 89 pounds); and Schenley last produced in 1952 (when total production was 25,426 pounds). J. T. Baker Chemical Co (consolidated by Vick Chemical Co. after 1941) and Monsanto, not shown on Table 13, entered the antibiotics industry after World War II and dropped out in 1953 and 1954, respectively. Both were relatively minor producers.

[2] Purchase by Bristol occurred during World War II.

Source: Civilian Production Administration, Industrial Statistics Division, War Industrial Facilities Authorized July 1940 through August 1945, Washington, July 30, 1946. FTC data request, 1957.

produced, and American Cyanamid (Lederle) produced an additional 20 percent of the total. In 1956 Pfizer produced 26.0 percent of the total volume and American Cyanamid 23.1 percent of the total. Among producers of penicillin, four companies accounted for nearly 80 percent of national output in 1955 and 82 percent in 1956. In 1955, Pfizer produced nearly 30 percent of the total; Merck, almost 20 percent; Olin Mathieson (Squibb), 17 percent; and Lilly about 13 percent. In 1956, Olin Mathieson produced 24.5 percent; Merck, 20 percent; Lilly, 19 percent; and Pfizer, 18.6 percent amounting to 82 percent of total penicillin production.

The antibiotics manufacturers, most of which operate within the ethical drug industry, maintain a close relationship with the medical profession and with retail pharmacists. Such changes in ownership as have occurred have not apparently disturbed this relationship. For example, Olin Mathieson which purchased Squibb in 1952 retained the Squibb name in the drug industry; Lederle continued to retain its trade-name identity after its purchase by American Cyanamid in 1931, as did Wyeth, purchased by American Home Products in 1931.

The 12 manufacturers of antibiotics which have remained in the industry since 1954 are—

Abbott Laboratories
American Cyanamid Co. (Lederle Laboratories)
American Home Products Corp. (Wyeth Laboratories)
Bristol-Myers Co.
Commercial Solvents Corp.

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Eli Lilly & Co.
Merck & Co., Inc.
Olin Mathieson Chemical Corp. (E. R. Squibb)
Parke Davis & Co.
S. B. Penick & Co.
Chas. Pfizer & Co., Inc.
The Upjohn Co.

Five of the companies in the above list carry on their operations through subsidiary companies or divisions in large diversified holding-operating company systems. The other seven may be characterized as being chiefly engaged in manufacturing and marketing pharmaceuticals. Accordingly, in the descriptions that follow, the companies will be grouped under two major headings:

1. Holding-operating diversified companies.
2. Firms which principally produce and sell pharmaceuticals.

Holding-operating diversified companies

Examples of holding-operating company systems are Olin Mathieson Chemical Corp., American Cyanamid Co., and American Home Products Corp., which control E. R. Squibb & Sons, Lederle Laboratories, and Wyeth Laboratories, respectively. Brief descriptions of these three firms, together with Bristol-Myers Co. and Commercial Solvents Corp., all of which might be considered as having widely diversified operations, are given below.

American Cyanamid Co. functions chiefly as an operating corporation, and as of December 31, 1956, it had about 20 wholly owned subsidiaries in addition to a number of affiliated companies. The parent and its system companies are engaged in the manufacture and sale of a widely diversified line of industrial and fine chemicals, surgical products, fibers, pigments, phosphates and nitrogen products, veterinary and garden products. Antibiotics, pharmaceuticals, biologicals, allergenic extracts, and diagnostic agents are manufactured in the Lederle Laboratories Division. American Cyanamid markets a line of about 400 pharmaceutical products. Plants are located in 20 States and in 6 foreign countries. In addition, plants for producing antibiotics and other pharmaceuticals have been constructed in Argentina, Brazil, and England. The company acquired the antibiotics division of Heyden Chemical Corp. (now Heyden Newport Chemical Corp.) in December 1953. As of December 31, 1954, the parent company reported an aggregate of 9,793 holders of the outstanding preferred stock and 38,558 common-stock holders.

American Home Products Corp. is a holding and management company with about 40 domestic and foreign subsidiaries engaged in the

manufacture and sales of ethical drugs, packaged drugs and cosmetics, food and household products. Antibiotics and other pharmaceutical products are manufactured by its Wyeth Laboratories subsidiary. It has foreign subsidiaries and branches located in Canada, England, India, Australia, New Zealand, Latin America, and Europe. A substantial plant addition for the production of streptomycin is being built in Brazil. As of December 31, 1956, this company had 13,482 employees and 20,831 stockholders. Forty-seven percent of its 1956 sales represented ethical drugs, 18 percent food, 18 percent packaged drugs and cosmetics, and 17 percent household products.

Bristol-Myers Co. functions as a holding-operating company, having a number of domestic and foreign subsidiaries engaged in the manufacture of molded plastic products, proprietary pharmaceutical specialties, antibiotics, and other drugs. The company's 1956 sales were composed of 66.7 percent proprietary preparations, 17.5 percent ethical drug preparations, 5.2 percent cosmetics, Fiberglas products and miscellaneous, and 10.6 percent metal tubes and brushes. Total consolidated sales in 1956 amounted to $89,403,544. This amount, however, does not include $10,650,000 of foreign sales. Consolidated assets, as of December 31, 1956, amounted to $57,504,534, of which $19,084,490 represented net property, plant, and equipment. Antibiotics, chemicals, and other pharmaceuticals are manufactured by Bristol Laboratories, Inc., located in Syracuse, N. Y. Some of the parent company's foreign operations are conducted through its operating division, Bristol-Myers International, which in turn has eight subsidiaries, located in Australia, New Zealand, Argentina, Brazil, Cuba, Mexico, England, and South Africa. The company's 1956 consolidated financial statements include the parent and all wholly owned North American subsidiaries. Dividends received from overseas unconsolidated subsidiaries are included in reported net earnings. The parent company's investment in and advances to its unconsolidated system companies, branches, and licensees is carried at $2,924,532 as of December 31, 1956. Foreign operations are also conducted by Bristol Laboratories, which has six subsidiaries, located in Canada, Colombia, England, Peru, Brazil, and South Africa.

Commercial Solvents Corp. is engaged in the manufacture and sale of industrial and agricultural chemicals, animal nutrition products, antibiotics and other pharmaceutical products, potable spirits and automotive specialties such as antifreeze and nitro fuel. This company has plants located in six States. Its wholly owned subsidiary, Commercial Distillers Corp., manufacturers whiskies and neutral spirits. It also has two affiliates, Northwest Nitro-Chemical, Ltd., and Thermatomic Carbon Co. As of December 31, 1956, there were 1,959 employees and 18,934 shareholders.

Olin Mathieson Chemical Corp. has approximately 40 subsidiaries, of which 36 are wholly owned. Its major operating companies are engaged in the manufacture and fabrication of aluminum, paper, copper and brass products. The parent company, through its numerous divisions, manufactures industrial and phosphate chemicals, arms, ammunition, explosives, film, drugs and pharmaceuticals (including antibiotics manufactured in its E. R. Squibb & Sons Division acquired in 1952). In 1956, consolidated sales were composed of 21.0 percent industrial chemicals; 17.5 percent film, paper, and forest products; 16.1 percent phosphate chemicals and plant foods; 16.7 percent arms, ammunitions, and explosives; 16.9 percent drugs and pharmaceuticals; and 11.8 percent metals. This company also has a number of affiliates engaged in industrial construction, shipping, aircraft, and rocket development. As of December 31, 1956, Olin Mathieson's common and preferred stockholders numbered approximately 53,000 and 1,800, respectively. There were about 42,000 employees of the consolidated companies as of the same date.

Firms which are principally pharmaceutical

In addition to the foregoing 5 companies, there are 7 other companies listed above which can be characterized as being chiefly pharmaceutical firms. All are operating companies with numerous overseas subsidiaries or affiliates conducting their foreign operations. These companies are briefly described below.

Abbott Laboratories, an Illinois corporation organized in 1900, conducts worldwide operations through 37 active wholly owned subsidiaries. This company is a leading domestic producer of pharmaceuticals, medicinal chemicals, bulk intravenous solutions, vitamins, and antibiotics. It also produces germicides, radioisotopes, and hypnotics. Consolidated assets in 1956 amounted to $102,572,422, of which $22,206,489 consisted of assets located in foreign countries. Approximately one-half of these foreign assets are in South America. Abbott has 17,497 stockholders and 3,100 employees. For the 12 months ended December 31, 1956, net sales amounted to $96,789,412, of which 23 percent represented foreign sales other than Canadian. More than 650 items are reported to be manufactured by the company.

Eli Lilly & Co. manufactures about 55 pharmaceutical and biological veterinary products. The company has eight wholly owned subsidiaries. One of its most recent acquisitions, Corn States Laboratories, Inc., at Omaha, Nebr., was purchased in April 1956. Another subsidiary is Paper Package Co., of Indianapolis, Ind., which manufactures paper and plastic containers. Other system companies operating through Eli Lilly International Corp. are located in England, Canada, Central and South America. The parent and subsidiaries

manufacture and sell antibiotics, vitamins, insulin, liver products, barbiturates, polio vaccine (amounting to $28,900,000 in 1956), animal nutrients, and other pharmaceuticals. The company has 4,800 common-stock holders and 8,872 employees. For the 12 months ended December 31, 1956, total consolidated net sales amounted to $181,529,751.

Merck & Co., Inc., was incorporated under the laws of the State of New Jersey in 1934. However, the firm was first established in the United States in 1891. In 1953 it acquired Sharp & Dohme, Inc., which is presently operated as a division. Merck has a number of domestic and foreign subsidiaries which own and operate manufacturing plants located in 5 States and 10 foreign countries. The company has four operating divisions three of which participate in the development, and domestic production and sales of pharmaceuticals, and biological specialties including antibiotics: Merck Sharp & Dohme Research Laboratories Division, Merck Sharp & Dohme Division and Merck & Co., Inc. Chemical Division. The 1956 consolidated net sales of $172,432,000 reflect sales of all wholly owned subsidiaries. Sales of all international operations, including direct export from the United States, amounted to $41 million, or 23 percent, of total company sales. The operations of foreign subsidiaries and branches resulted in net income of $3,700,000 in 1956, of which $818,000 was remitted to the United States. The above amounts do not include profits of the parent company and domestic subsidiaries and branches. The amount of net assets included in the consolidated balance sheet as of December 31, 1956, representing foreign subsidiaries and branches, was $20,676,000, of which $5,664,853 consisted of net fixed plant and property.

Parke, Davis & Co. was organized as a Michigan corporation in 1875. It functions chiefly as an operating company. There are, however, 10 wholly owned subsidiaries operating in a number of foreign countries, including Italy, Argentina, Cuba, Canada, and Mexico. The 1956 consolidated net sales amounted to $134,093,000, of which $91,492,000 were derived from the United States and Canada, $15,404,000 from other Western Hemisphere countries and $27,197,000 from other world trade. The company reports that it produces over 600 products bearing the firm label. In addition to being a manufacturer of antibiotics, the firm is one of the largest manufacturers and distributors of pharmaceuticals, including vitamins, antihistaminic agents, vaccines, and hormones. As of December 31, 1956, it had 25,457 stockholders and 9,849 employees, including nearly 4,000 abroad. Consolidated net assets in 1956 amounted to $139,262,405, of which $29,479,000 were located in foreign countries.

S. B. Penick & Co., which was incorporated under Delaware laws in December 1931, manufactures fine chemicals, bulk pharmaceuticals,

antibiotics, synthetic and aromatic chemicals, essential oils and related products, insecticides, soluble gums, and other products. The firm is also engaged in the milling of imported and domestic crude botanical drugs. It maintains plants and warehouses in 5 cities and has sales representation in 11 large cities. The company has five wholly owned subsidiaries. The majority of the voting control is closely held by the Penick family group. As of May 31, 1956, consolidated assets amounted to about $14.2 million, and net consolidated sales for the 12 months ending May 31, 1956, were $19.7 millions.

Chas. Pfizer & Co., Inc., manufactures and sells fine organic chemicals, and is a leading manufacturer of antibiotics and other pharmaceuticals. Domestic plants and laboratories are located in Brooklyn, N. Y., Groton, Conn., Terre Haute, Ind., and Maywood, N. J. The 1956 financial statements include the parent and subsidiary companies, all of which are wholly owned. The net assets of foreign subsidiaries and branches together with the foreign assets of domestic subsidiaries amounted to $34,208,837 in 1956. Total consolidated assets as of the same date were $152,582,685. The parent, through its wholly owned subsidiary Pfizer Corp., conducts operations in 13 foreign countries, including England, Japan, Germany, Canada, Brazil, and France. A new fermentation plant constructed in England and another in France began operating in 1956. A fermentation plant was also opened in Japan that year. A continuation of the firm's expansion program, including manufacturing facilities, is also being carried out in other parts of the world. This program involves expenditures between $20 million and $25 million over the next 2 years. Sales and earnings in 1956 were reported to be the highest in the 108-year history of the firm. One-third of the company's 1956 total sales were accounted for by its international subsidiaries, 32 percent of sales were accounted for by Pfizer's Laboratories Division which manufactures antibiotics and other pharmaceuticals, 21 percent by its Chemical Division, 8 percent by the Agricultural Division, and 6 percent by the J. B. Roerig & Co. Division which manufactures vitamins and other pharmaceutical products.

The Upjohn Co., which started as a partnership in 1884, was incorporated in Michigan in 1909. The firm presently manufactures over 800 pharmaceutical products bearing the company name. Sales are made through regular trade channels, including wholesalers, druggists, hospitals, and physicians. Total employees number about 5,000, of which 750 are salesmen. Inventories are carried in 16 large cities. The company has been largely under the control and management of the Upjohn family since inception. Under its guidance, there has been a gradual broadening of products handled, which has aided

the firm in achieving and maintaing its position as one of the leading drug manufacturers. The company has five subsidiaries, located in Canada, England, Brazil, Mexico, and Australia. As of December 31, 1956, total assets amounted to $107.8 million, of which $48.8 million represented property, plant, and equipment. Net sales for 1956 were $111.0 million.

The antibiotic products in which each manufacturer specializes are recounted in the following section. The plants operated by each company are described in a later section in this chapter.

Products of Each Manufacturer

Each manufacturer of antibiotics usually produces several basic substances. Table 14 lists the 12 manufacturers and the substances produced by each in 1956. Pfizer produced 14 different substances, Merck 9, Olin Mathieson 7, and Lilly produced 6. Other company totals ranged from 1 to 5.

Table 14 indicates that 17 of the 29 antibiotic substances produced in 1956 were manufactured by 1 company each; 4 by 2 companies; 2

TABLE 14.—*Antibiotics producers and products made in 1956*

Antibiotic substance	Abbott	American Cyanamid	American Home Products	Bristol	Commercial Solvents	Lilly	Merck	Olin Mathieson	Parke, Davis	Penick	Pfizer	Upjohn	Total companies
Penicillins:													
Potassium	x		x	x		x	x	x			x		7
Sodium							x	x			x		3
Procaine	x		x	x		x	x	x			x		7
Aluminum											x		1
Benzathine			x								x		2
"O" chloroprocaine												x	1
"V"						x							1
"V" hydrabamine	x												1
"V" benzathine			x										1
"V" potassium	x												1
"O" sodium												x	1
Other antibiotics:													
Streptomycin		x				x	x	x			x		5
Dihydrostreptomycin		x				x	x	x			x		5
Bacitracin					x		x			x	x		4
Chlortetracycline		x											1
Chloramphenicol									x				1
Tyrothricin										x			1
Oxytetracycline											x		1
Viomycin											x		1
Neomycin		x					x	x		x	x	x	6
Polymyxin											x		1
Erythromycin	x					x							2
Tetracycline		x		x							x		3
Nystatin								x					1
Cycloserine					x		x						2
Amphomycin				x									1
Oleandomycin											x		1
Novobiocin				x			x					x[1]	2
Candicidin										x			1
Total products made by each company	5	5	4	5	2	6	9	7	1	4	14	4	

[1] Bristol manufactured Novobiocin for Upjohn on a toll basis.

Source: FTC data request, 1957.

by 3 companies; 1 by 4 companies; 2 by 5 companies, 1 by 6 companies; and 2 by 7 companies. Thus, nearly three-fifths of all antibiotic substances produced in 1956 were one-company products. This represents a distinct change in individual company control of products from that prevailing in 1948, when only 4 of the penicillins and other antibiotics, for which output was reported, were produced by only 1 company, and 7 were produced by more than 1 company. Thus, comparing 1948 with 1956, the number produced as one-company products increased from 4 to 17, while the number produced by more than one company increased from 7 to 12.

The number of different kinds of antibiotics substances which each of the 12 manufacturers produce are summarized for 1948 and 1956 in table 15. The table shows that most companies are producing about

TABLE 15.—*Kinds of antibiotics produced by each manufacturer: 1948 and 1956*

Company	1948		1956	
	Penicillin	Other	Penicillin	Other
Abbott	4	1	4	1
American Cyanamid	3	1	0	5
American Home Products	3	0	4	0
Bristol-Myers	3	1	2	[1]3
Commercial Solvents	3	1	0	2
Eli Lilly	2	2	3	3
Merck	2	1	3	6
Olin Mathieson	3	1	3	4
Parke, Davis	0	1	0	1
S. B. Penick	0	0	0	4
Chas. Pfizer	4	2	5	9
Upjohn	4	1	2	2

[1] Bristol actually produced 3 "other" antibiotics. Novobiocin was manufactured for Upjohn on a toll basis.

Source: FTC data requests, 1956 and 1957.

TABLE 16.—*Number of manufacturers of antibiotics produced: 1956*

Antibiotics produced by—		
1 company	2 or 3 companies	More than 3 companies
Penicillin aluminum.[1]	Penicillin sodium.	Penicillin potassium.
Penicillin "O" chloroprocaine.[1]	Penicillin benzathine.	Penicillin procaine.
Penicillin "V."	Erythromycin.	Streptomycin.
Penicillin "V" hydrabamine.[1]	Tetracycline.	Dihydrostreptomycin.
Penicillin "V" potassium.[1]	Cycloserine.	Bacitracin.
Penicillin "V" benzathine.	Novobiocin.	Neomycin.
Penicillin "O" sodium.[1]		
Chlortetracycline.		
Chloramphenicol.		
Tyrothricin.		
Oxytetracycline.		
Viomycin.		
Polymyxin.[1]		
Nystatin.[1]		
Amphomycin.		
Oleandomycin.		
Candicidin.[1]		

[1] The single manufacturer does not hold a patent on this product. In cases where patents are involved, they are held by companies or institutions not engaging in the manufacture of the item.

Source: FTC data request, 1957.

the same number of penicillins as they did in 1948 (except for American Cyanamid and Commercial Solvents, which had discontinued penicillin production by 1956), and that most companies have significantly increased the number of other antibiotic substances produced. In 1948, Lilly and Pfizer led with 2 other substances, and by 1956 Pfizer led in diversification with 9 other substances, Merck followed with 6 other substances, American Cyanamid with 5, and Olin Mathieson and Penick were each producing 4 other substances.

The antibiotic substances manufactured in 1956 according to the numbers of manufacturers of each are listed in table 16.

Manufacturers classified according to "exclusive" and "semiexclusive" items which they produce are listed in table 17. The company which leads in the manufacture of antibiotics of which it is the exclusive producer is Pfizer with five exclusive products.

TABLE 17.—*"Exclusive" and "semiexclusive" antibiotics manufactured by each company: 1956*

Name of company	"Exclusive" products, manufactured by no other company	"Semiexclusive" products, manufactured by one or two other companies
Abbott	Penicillin "V" hydrabamine. Penicillin "V" potassium.	Erythromycin.
American Cyanamid (Lederle)	Chlortetracycline.	Tetracycline.
American Home Products (Wyeth)	Penicillin "V" bensathine.	Penicillin benzathine.
Bristol-Myers	Amphomycin.	Tetracycline. Novobiocin.[1]
Commercial Solvents		Cycloserine.
Eli Lilly	Penicillin "V."	Erythromycin.
Merck		Penicillin sodium. Novobiocin. Cycloserine.
Olin Mathieson (Squibb)	Nystatin.	Penicillin sodium.
Parke, Davis	Chloramphenicol.	
Penick	Tyrothricin. Candicidin.	
Pfizer	Penicillin aluminum. Oxytetracycline. Viomycin. Polymyxin. Oleandomycin.	Penicillin bensathine. Penicillin sodium. Tetracycline.
Upjohn	Penicillin "O" chloroprocaine. Penicillin "O" sodium.	Novobiocin.[1]

[1] Bristol manufactured Novobiocin for Upjohn on a toll basis. Upjohn did not produce any.

Source: FTC data request, 1957.

The summarization in table 18 groups the companies producing semiexclusive items.

TABLE 18.—*Companies producing the same semiexclusive products: 1956*

Product	Manufacturers
Penicillin sodium	Merck; Pfizer; Olin Mathieson.
Novobiocin [1]	Merck; Upjohn; Bristol.
Cycloserine	Merck; Commercial Solvents.
Erythromycin	Abbott; Lilly.
Penicillin benzathine	American Home; Pfizer.
Tetracycline	Pfizer; American Cyanamid; Bristol.

[1] Merck and Bristol produced this item. All Bristol's production was manufactured on a toll basis for Upjohn.

Source: FTC data request, 1957.

Specialization is apparently related to profitability of operation. Merck states, "* * * profit on products developed by a particular company and identified with it tends to be more stable than on products of general manufacture." [8] In 1951 Pfizer stated, "The higher margins of profit on antibotics (during the past several years the average profit margin on antibiotics has been greater than the average profit margin on all products) has resulted from introduction of several new specialties * * *" [9] American Cyanamid, in 1950, stated that the higher margin of profits resulted from new specialties, "the latest and most important of which is Aureomycin [chlortetracycline]." [10]

In the early years of the industry, only a few antibiotic substances had been developed, and most manufacturers produced most if not all of the 4 or 5 principal products. Later, as research led to new products, each company tended to develop its own antibiotic line.

Both the number of manufacturers in the antibiotics industry and the number of companies producing any one item have tended to decline in recent years. There were 17 antibiotic manufacturers in the 1949–1952 period, but in the 1954–56 period, the industry was represented by only 12 manufacturers. Of 14 producers of procaine penicillin in 1948, only 7 manufactured this substance in 1956.

The number of manufacturers of each antibiotic which has been produced commercially from 1948 to 1956, and the total number of manufacturers in each of these years is shown in table 19. As the total number of manufacturers decreased, the table reveals that the number of antibiotics being manufactured increased. At the same time, the volume of output of all antibiotics also increased (tables 8 and 9). The total output by 12 manufacturers in 1956 was nearly 7 times the total output of 17 manufacturers in 1949, and over 10 times the output of 16 manufacturers in 1948.

In 1948, the industry concentrated on 5 principal products—4 penicillins and streptomycin. Fourteen of the 16 manufacturers in that year produced procaine penicillin, the major volume product of the industry in 1948 as well as in 1956. While 14 manufacturers produced 36,000 BU in 1948, 13 companies produced over 200,000 BU in 1952 and 7 companies produced over 350,000 BU in 1956. A relatively new product, benzathine penicillin, was produced by 4 firms in 1953, when output totaled 22,000 BU. In 1956, only two companies produced the same output.

Thus, while the number of manufacturers has decreased since 1948, the number of products and the total production of antibiotics has greatly increased.

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[8] Merck proxy statement, April 30, 1953, p. 9.
[9] Pfizer prospectus dated June 26, 1951, p. 6.
[10] American Cyanamid prospectus, May 18, 1950, p. 8.

TABLE 19.—*Number of manufacturers of each antibiotic: 1948 to 1956*

Antibiotic	1948	1949	1950	1951	1952	1953	1954	1955	1956
Penicillin salts:									
Triethylamine	1	----	1	----	----	----	----	----	----
Calcium	9	3	1	1	1	----	----	----	----
Potassium	6	13	13	12	13	11	11	9	7
Sodium	12	9	7	8	8	6	6	5	3
Procaine	14	14	13	13	13	11	10	9	7
Aluminum	----	1	1	1	1	----	1	1	1
Ephedrine	----	1	----	----	----	----	----	----	----
1-Ephenamine	----	----	----	1	1	----	1	----	----
"O" Potassium	----	----	----	1	1	----	----	----	----
Benzathine	----	----	----	1	3	4	2	2	2
"O" Chloroprocaine	----	----	----	----	----	1	1	1	1
"V"	----	----	----	----	----	----	----	2	1
"V" Hydrabamine	----	----	----	----	----	----	----	----	1
"V" Potassium	----	----	----	----	----	----	----	----	1
"V" Benzathine	----	----	----	----	----	----	----	----	1
"O" Sodium	----	----	----	----	----	----	----	----	1
Streptomycin	8	8	7	7	7	6	7	6	5
Dihydrostreptomycin	2	7	7	7	6	7	7	6	5
Bacitracin	1	1	1	2	3	3	3	4	4
Chlortetracycline	1	1	1	1	1	1	1	1	1
Chloramphenicol	1	2	2	2	2	2	1	1	1
Tyrothricin	----	1	1	1	1	1	----	1	1
Oxytetracycline	----	----	1	1	1	1	1	1	1
Viomycin	----	----	1	1	1	1	1	1	1
Neomycin and salts	----	----	----	2	2	3	5	5	6
Polymyxin	----	----	----	1	1	1	1	1	1
Actidione	----	----	----	----	1	1	1	1	----
Erythromycin	----	----	----	----	2	3	3	2	2
Fumagillin	----	----	----	----	1	1	1	----	----
Carbomycin	----	----	----	----	----	1	----	1	----
Tetracycline	----	----	----	----	----	2	3	3	3
Nystatin	----	----	----	----	----	----	1	1	1
Anisomycin	----	----	----	----	----	----	----	1	----
Cycloserine	----	----	----	----	----	----	----	1	2
Amphomycin	----	----	----	----	----	----	----	----	1
Novobiocin	----	----	----	----	----	----	----	----	[1] 2
Oleandomycin	----	----	----	----	----	----	----	----	1
Candicidin	----	----	----	----	----	----	----	----	1
Total manufacturers	16	17	17	17	17	15	12	12	12

[1] Merck and Bristol produced Novobiocin. Bristol produced for Upjohn on a toll basis.

Source: FTC data requests, 1956 and 1957.

As has been stated, each company has tended to develop its own product line of antibiotics. In table 20, the relative importance of each of the principal products of each manufacturer to his total are shown in the first column of the table for 2 years, 1950 and 1956. As the table reveals, most of the products which were major revenue producers in 1950 had been replaced by a new antibiotic in 1956.

In 1950, procaine penicillin was the principal revenue item of 9 of the 17 companies in the industry—Abbott, American Home Products, Bristol-Myers, Lilly, Olin Mathieson, Upjohn, Cutter, Schenley, and Vick. By 1956, 5 of these companies had moved to new principal products, 3 had ceased all antibiotics manufacturing, and only 1 still retained procaine penicillin as its principal antibiotic product.

Chlortetracycline, introduced by American Cyanamid in 1948, was the company's only product in that year; by 1956 this item represented less than 40 percent of the company's revenue, while a new product, tetracycline, was the most important.

TABLE 20.—*Percentage distribution of antibiotics manufacturers' products—each product stated as a percentage of (1) each manufacturer's total, (2) national product total, and (3) national total of all products—based on dollar sales of own production: 1950–56* [1]

Manufacturer and product	Each product as a percentage of—					
	(1) Each manufacturer's total		(2) National product total		(3) National total of all products	
	1950	1956	1950	1956	1950	1956
Abbott	100.0	100.0			2.7	1.1
Penicillin procaine	55.4	22.4	5.9	2.9	1.5	.3
Penicillin potassium	44.6	3.5	7.2	.8	1.2	(2)
Erythromycin		64.2		11.5		.7
Penicillin "V" hydrabamine		9.7		100.0		.1
Fumagillin		.2		100.0		(2)
American Cyanamid (Lederle)	100.0	100.0			26.6	28.1
Chlortetracycline	100.0	39.8	100.0	100.0	26.6	11.2
Tetracycline		58.6		68.2		16.5
Dihydrostreptomycin		.8		4.1		.2
Neomycin		.7		5.6		.2
Streptomycin		.1		.8		(2)
American Home (Wyeth)	100.0	100.0			1.8	5.0
Penicillin procaine	99.3	12.6	7.2	7.5	1.8	.6
Penicillin potassium	.7	6.3	.1	6.7	(2)	.3
Penicillin benzathine		67.7		98.6		3.4
Penicillin "V" benzathine		12.2		100.0		.6
Penicillin "V"		1.2		1.4		.1
Bristol-Myers	100.0	100.0			6.0	4.3
Penicillin procaine	63.4	14.0	15.2	7.1	3.8	.6
Penicillin potassium	32.5	2.5	11.7	2.3	1.9	.1
Pencillin sodium	4.1		6.3		.3	
Tetracycline		83.4		14.8		3.6
Amphomycin		.1		100.0		(2)
Commercial Solvents	100.0	100.0			2.5	.4
Penicillin potassium	45.5	.3	6.9	(2)	1.1	(2)
Penicillin procaine	29.8	2.0	3.0	.1	.7	(2)
Bacitracin	22.8	91.2	100.0	51.5	.6	.4
Penicillin sodium	1.9		1.3		.1	
Cycloserine		6.1		9.7		(2)
Penicillin 1-ephenamine		.4		100.0		(2)
Eli Lilly	100.0	100.0			11.0	11.7
Penicillin procaine	47.7	9.0	21.1	12.4	5.2	1.1
Penicillin potassium	45.2	2.6	30.0	6.6	5.0	.3
Penicillin sodium	4.3		12.0		.5	
Streptomycin	2.1	1.0	6.7	5.7	.2	.1
Dihydrostreptomycin	.7	5.6	.6	10.8	.1	.7
Erythromycin		45.3		87.5		5.3
Penicillin "V"		34.4		98.6		4.0
Cycloserine		2.1		89.7		.2
Merck & Co	100.0	100.0			11.0	7.2
Dihydrostreptomycin	44.4	24.2	41.5	28.9	4.9	1.8
Streptomycin	17.1	7.3	53.7	26.4	1.9	.5
Penicillin sodium	21.5	3.2	59.4	37.8	2.4	.2
Penicillin procaine	13.2	20.7	5.8	17.6	1.4	1.5
Penicillin potassium	3.8	10.7	2.5	16.3	.4	.8
Neomycin		22.5		44.9		1.6
Novobiocin		11.0		36.2		.8
Bacitracin		.4		3.3		(2)
Cycloserine		(2)		.6		(2)
Olin Mathieson (Squibb)	100.0	100.0			10.8	6.7
Penicillin procaine	54.4	29.0	23.4	22.8	5.9	1.9
Penicillin potassium	30.3	26.2	19.7	37.4	3.3	1.8
Dihydrostreptomycin	13.0	16.9	12.0	18.6	1.4	1.1
Streptomycin	2.3	11.8	6.9	39.2	.2	.8
Nystatin		9.6		100.0		.6
Neomycin		3.6		6.8		.3
Penicillin sodium		2.9		30.8		.2
Parke, Davis	100.0	100.0			5.9	7.3
Chloramphenicol	100.0	100.0	77.6	100.0	5.9	7.3

See footnotes at end of table.

Table 20.—*Percentage distribution of antibiotics manufacturers' products*—Con.

Manufacturer and product	Each product as a percentage of— (1) Each manufacturer's total		(2) National product total		(3) National total of all products	
	1950	1956	1950	1956	1950	1956
Penick	100.0	100.0	---	---	.1	.4
Tyrothricin	100.0	17.9	100.0	100.0	.1	.1
Bacitracin	---	58.8	---	25.6	---	.2
Neomycin	---	23.0	---	2.1	---	.1
Candicidin	---	.3	---	100.0	---	(2)
Pfizer	100.0	100.0	---	---	11.7	23.4
Oxytetracycline	36.7	51.3	100.0	100.0	4.3	12.0
Dihydrostreptomycin	34.8	9.7	34.8	37.6	4.1	2.3
Penicillin potassium	9.1	1.9	6.4	9.5	1.1	.4
Penicillin procaine	8.2	9.0	3.9	24.8	.9	2.1
Streptomycin	5.9	2.4	20.1	27.9	.7	.6
Penicillin sodium	4.8	.7	14.1	28.1	.6	.2
Penicillin aluminum	.4	(2)	100.0	100.0	(2)	(2)
Viomycin	.1	1.0	100.0	100.0	(2)	.2
Tetracycline	---	17.5	---	17.0	---	4.1
Oleandomycin	---	4.2	---	100.0	---	1.0
Polymyxin	---	1.3	---	100.0	---	.3
Bacitracin	---	.6	---	19.6	---	.2
Neomycin	---	.2	---	1.2	---	(2)
Penicillin benzathine	---	.2	---	1.4	---	(2)
Carbomycin	---	(3)	---	100.0	---	(2)
Upjohn	100.0	100.0	---	---	.7	4.4
Penicillin procaine	58.3	9.4	1.7	4.8	.4	.4
Penicillin potassium	28.9	21.8	1.3	20.4	.2	1.0
Dihydrostreptomycin	9.1	---	.6	---	.1	---
Streptomycin	3.7	---	.8	---	(2)	---
Penicillin calcium	(2)	---	25.3	---	(2)	---
Neomycin	---	32.6	---	39.4	---	1.4
Novobiocin	---	32.0	---	63.8	---	1.4
Penicillin "O" chloroprocaine	---	1.8	---	100.0	---	.1
Erythromycin	---	1.3	---	1.0	---	.1
Penicillin sodium	---	.5	---	3.3	---	(2)
Penicillin "O" sodium	---	.4	---	100.0	---	(2)
Penicillin "O" potassium	---	.2	---	100.0	---	(2)
Cutter	100.0	---		---	.7	---
Penicillin procaine	73.2	---	2.0	---	.5	---
Penicillin potassium	26.8	---	1.1	---	.2	---
Heyden	100.0	---		---	2.8	---
Dihydrostreptomycin	32.3	---	7.8	---	.9	---
Penicillin potassium	31.6	---	5.4	---	.9	---
Penicillin procaine	23.4	---	2.0	---	.6	---
Streptomycin	7.2	---	5.9	---	.2	---
Penicillin sodium	5.5	---	4.0	---	.2	---
Penicillin calcium	(2)	---	74.7	---	(2)	---
Hoffmann-La Roche [3]	100.0	---		---	(2)	---
Penicillin ephedrine	100.0	---	100.0	---	(2)	---
Monsanto	100.0	---		---	1.7	---
Chloramphenicol	100.0	---	22.4	---	1.7	---
Schenley	100.0	---		---	3.2	---
Penicillin procaine	44.6	---	5.7	---	1.5	---
Penicillin potassium	38.2	---	7.3	---	1.2	---
Dihydrostreptomycin	10.1	---	2.7	---	.3	---
Streptomycin	6.5	---	5.9	---	.2	---
Penicillin triethylamine	.6	---	100.0	---	(2)	---
Vick	100.0	---		---	.8	---
Penicillin procaine	76.8	---	---	---	.6	---
Penicillin sodium	14.9	---	---	---	.1	---
Penicillin potassium	8.3	---	---	---	.1	---
Total	---	---	---	---	100.0	100.0

[1] Includes carryover from previous year in some instances.
[2] Less than 0.05 percent.
This company was not a producer in 1950 but sold penicillin previously produced.

Manufacturers' Shares of the Market

With respect to tetracycline (first produced in 1953), three companies shared the producers' market for this item in 1956, as follows from table 20, column 2:[11]

Company:	*Percent of tetracycline market*
American Cyanamid	68. 2
Pfizer	17. 0
Bristol-Myers	14. 8
Total	100. 0

But while Cyanamid's sales of tetracycline represented 68.2 percent of the total sales by manufacturers of tetracycline, this sale of tetracycline represented only 16.5 percent of all sales (from manufacturers' production) of antibiotics for the year.

The 16.5 percent of total sales represented by Cyanamid's sales of tetracycline is the largest share that any single product of any single company had in the antibiotics market in 1956.

The shares of the producing companies in the total antibiotics market in 1950 and 1956, as shown in table 20, column 3, of the table were:

Company	Percent share of total antibiotics market	
	1950	1956
American Cyanamid	26. 6	28. 1
Pfizer	11. 7	23. 4
Eli Lilly	11. 0	11. 7
Parke Davis	5. 9	7. 3
Merck	11. 0	7. 2
Olin Mathieson	10. 8	6. 7
American Home Products	1. 8	5. 0
Upjohn	. 7	4. 4
Bristol-Myers	6. 0	4. 3
Abbott	2. 7	1. 1
Commercial Solvents	2. 5	. 4
Penick	0. 1	. 4
Others	9. 2	0
	100. 0	100. 0

As shown in table 20, in 1950, chlortetracycline (produced only by Cyanamid) accounted for 26.7 percent of all sales of all manufacturers from own production. In 1956, the largest share of any product was held by tetracycline (made by three companies), which accounted for 24.2 percent of the total market. During the period from 1950 to 1956, the principal value item shifted from chlortetracycline to tetracycline, and the control of the principal item moved from the 1 producer of chlortetracycline in 1950 to 3 producers of tetracycline in 1956.

[11] Two additional manufacturers were licensed to sell the item, as explained in detail in ch. VIII.

United States Plant Locations and Ownership

Nineteen antibiotics manufacturing plants operated in 9 States in 1956 to produce a substantial portion of the world's output of antibiotics substances. Most of these plants combined processing and packaging with production facilities. In addition to the plants operated by the 12 United States manufacturers, a number of separate packaging (and processing) facilities were operated by nonmanufacturers. The plants dealt with in the ensuing discussion are limited to those that were established by manufacturers.

Ownership of manufacturing facilities has shown some change since World War II (see table 13, Status of World War II Manufacturers), but no major producers of antibiotics have dropped out of the industry. Of the 20 authorized wartime producers, 17 were operating in 1950, and by 1954, 5 additional firms dropped out, leaving 12 manufacturers in the industry. Table 21 shows the States in which the 17 producers in 1950 and the 12 remaining producers in 1956 maintained manufacturing facilities.

In 1956, combined manufacturing and packaging plants were located in 8 States (New Jersey, New York, Indiana, Illinois, Michigan, Pennsylvania, Virginia, and Connecticut), 2 additional States (Missouri and Iowa) had packaging plants which were operated by manufacturers, and West Virginia had a manufacturing plant which had no packaging facilities. The plant location information, previously presented in the description of individual companies, is summarized for antibiotics operations in table 21, which lists the owners of these antibiotics plants, and shows the States in which they are located for 2 recent years—1950 and 1956. During the period from 1950 to 1956, 20 manufacturing plants had been reduced to 19; and manufacturers' facilities for processing and packaging had been increased from 23 to 25.

While five manufacturers listed on table 21 for 1950 had ceased antibiotics production by 1956, the remaining manufacturers were expanding their production and processing facilities. Those dropping out during the period were Heyden (the antibiotics operations of Heyden were purchased by American Cyanamid which continued the manufacture of antibiotics), Schenley, Monsanto, J. T. Baker (a subsidiary of Vick Chemical Company), and Cutter. At the same time, American Cyanamid expanded its operations when it commenced manufacturing in New Jersey (with the acquired Heyden facilities) and in West Virginia, in addition to its New York antibiotics operations. Parke, Davis constructed an additional plant for manufacturing and packaging in Michigan. Lilly built a new manufacturing plant in Indiana. Merck built a new manufacturing and packaging plant in

TABLE 21.—*Location and ownership of domestic antibiotics manufacturing and packaging plants, 1950 and 1956*

Company	Year	California		Connecticut		Illinois		Indiana		Iowa		Michigan		Missouri		New Jersey		New York		Pennsylvania		Virginia		West Virginia		Total per company	
		Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging
Abbott	1950	---	---	---	---	1	1	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1
	1956	---	---	---	---	1	1	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1
American Cyanamid	1950	---	---	---	---	---	---	---	---	---	---	---	---	---	---	0	0	1	1	---	---	---	---	0	0	1	1
	1956	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1	1	1	---	---	---	---	1	0	3	2
Heyden [1]	1950	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1	---	---	---	---	---	---	---	---	1	1
	1956	---	---	---	---	---	---	---	---	---	---	---	---	---	---	(1)	(1)	---	---	---	---	---	---	---	---	0	0
American Home Products	1950	---	---	---	---	---	---	---	---	0	1	---	---	---	---	---	---	---	---	1	2	---	---	---	---	1	3
	1956	---	---	---	---	---	---	---	---	0	1	---	---	---	---	---	---	---	---	1	2	---	---	---	---	1	3
J. T. Baker [2]	1950	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1	---	---	---	---	---	---	---	---	1	1
	1956	---	---	---	---	---	---	---	---	---	---	---	---	---	---	(2)	(2)	---	---	---	---	---	---	---	---	0	0
Bristol	1950	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1	---	---	---	---	---	---	1	1
	1956	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1	---	---	---	---	---	---	1	1
Commercial Solvents	1950	---	---	---	---	0	1	1	1	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	2
	1956	---	---	---	---	0	1	1	1	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	2
Cutter Laboratories [3]	1950	1	1	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1
	1956	(3)	(3)	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	0	0
Lilly	1950	---	---	---	---	---	---	1	1	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1
	1956	---	---	---	---	---	---	2	1	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	2	1
Merck	1950	---	---	---	---	---	---	---	---	---	---	---	---	0	0	1	1	---	---	0	2	1	0	---	---	2	3
	1956	---	---	---	---	---	---	---	---	---	---	---	---	0	1	0	1	---	---	1	3	1	1	---	---	2	6
Monsanto [3]	1950	---	---	---	---	---	---	---	---	---	---	---	---	1	1	---	---	---	---	---	---	---	---	---	---	1	1
	1956	---	---	---	---	---	---	---	---	---	---	---	---	(3)	(3)	---	---	---	---	---	---	---	---	---	---	0	0
Olin Mathieson	1950	---	---	---	---	---	---	---	---	---	---	---	---	---	---	0	0	0	0	---	---	---	---	---	---	0	0
	1956	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1	0	1	---	---	---	---	---	---	1	2
Squibb [4]	1950	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1	0	1	---	---	---	---	---	---	1	2
	1956	---	---	---	---	---	---	---	---	---	---	---	---	---	---	(4)	(4)	---	---	---	---	---	---	---	---	0	0
Parke, Davis	1950	---	---	---	---	---	---	---	---	---	---	1	1	---	---	---	---	---	---	---	---	---	---	---	---	1	1
	1956	---	---	---	---	---	---	---	---	---	---	2	2	---	---	---	---	---	---	---	---	---	---	---	---	2	2
Penick	1950	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1	---	---	---	---	---	---	---	---	1	1
	1956	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1	---	---	---	---	---	---	---	---	1	1
Pfizer	1950	---	---	1	0	---	---	1	0	---	---	---	---	---	---	---	---	1	1	---	---	---	---	---	---	3	1
	1956	---	---	1	1	---	---	1	1	---	---	---	---	---	---	---	---	1	1	---	---	---	---	---	---	3	3
Schenley [3]	1950	---	---	---	---	---	---	1	1	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	1	1
	1956	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	0	0
Upjohn	1950	---	---	---	---	---	---	---	---	---	---	1	1	---	---	---	---	---	---	---	---	---	---	---	---	1	1
	1956	---	---	---	---	---	---	---	---	---	---	1	1	---	---	---	---	---	---	---	---	---	---	---	---	1	1
Total by States	1950	1	1	1	0	1	2	4	3	0	1	2	2	1	1	5	5	3	4	1	4	1	0	0	0	20	23
	1956	0	0	1	1	1	2	4	3	0	1	3	3	0	1	3	4	3	4	2	5	1	1	1	0	19	25

[1] American Cyanamid purchased the antibiotics division of Heyden Chemical Corp. in 1953. [2] Controlled by Vick Chemical Corp. which discontinued antibiotics manufacture in 1953. [3] Discontinued antibiotics manufacture in 1953. [4] Purchased in 1952 by Mathieson Chemical Corp., predecessor to Olin Mathieson Chemical Corp.

Source: FTC data request, 1957.

Pennsylvania, added packaging facilities to its Virginia plant, and commenced packaging in Missouri. Pfizer added packaging facilities to its Indiana and Connecticut plants.

Antibiotics plants usually extend over large areas, sometimes surrounded by several hundred acres of land. Penicillin plants constructed during World War II ranged up to about $3,500,000 in cost, but during the Korean action manufacturing plants costing as much as $16,500,000 were authorised in connection with the defense program. Present domestic installations are of even larger dimensions. A plant in Pennsylvania, valued at $26 million, is located on 180 acres of land.[12] A New York plant occupies 45 buildings on 440 acres.[13] An antibiotics manufacturing plant in Indiana, where no finishing or packaging operations are carried on, was built at a cost of about $20 million.[14] Another antibiotics plants, located in New Jersey, occupies more than 150 buildings situated on 200 acres of land.[15]

Foreign Plants Reported by United States Manufacturers

Following the boom in domestic plant expansion during the Korean war, the antibiotics companies began to accelerate the construction of foreign facilities, principally those for packaging the increased output of domestic manufacturing plants. During the 1950–1956 period, 52 new facilities were reported by United States manufacturers. Only 15 of these were supported by facilities for manufacturing; the remaining 37 were processing and packaging plants which relied on bulk or semiprocessed antibiotics from other sources.

The location of the antibiotics portion of the foreign facilities referred to previously in the description of the individual companies is summarized in table 22. This table shows the worldwide scope of antibiotics operations of United States producers. By 1956, 19 combination manufacturing and packaging plants and 37 other packaging plants were located in 12 countries; 21 packaging facilities were located in an additional 10 countries. In all, 10 United States manufacturers had established 77 foreign facilities for either manufacturing or packaging or both by 1956.

Aside from plants constructed abroad, American industry entered into a number of agreements to provide technological assistance to foreign antibiotics manufacturers.[16]

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[12] Merck annual report, 1951, p. 5; Merck prospectus, dated April 30, 1955, p. 11.

[13] American Cyanamid prospectus, dated May 21, 1952, p. 2.

[14] Eli Lilly annual report, 1951, p. 3; and for 1953, p. 3; Lilly executives' statement to Federal Trade Commission officials in 1957.

[15] Merck & Co., Inc., Chemical and Engineering News, vol. 35, No. 14, pt. II, April 8, 1957, p. 45.

[16] ECA Release No. 1137, December 28, 1949; ECA Advance Release No. 1653, August 10, 1950; MSA Advance Release No. 30, March 6, 1952; "Pushing for Production," Chemical Week, September 17, 1953, p. 31; FOA Advance Release No. 112, May 24, 1954.

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TABLE 22.—*Location of antibiotics plants or facilities in foreign countries established, owned or operated (in whole or in part) by American manufacturers: 1950 and 1956*

Country	Year	Abbott		American Cyanamid		American Home Products		Bristol		Lilly		Merck		Squibb-Olin Mathieson [1]		Parke, Davis		Pfizer		Upjohn		Total by country	
		Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging	Manufacturing	Packaging
Canada	1950		1			1	2				1	1	1		1		1					2	7
	1956		1	1	1	0	2		1		1	1	1		1		1		1		1	2	11
England	1950				1								1			1	1					1	3
	1956		1	1	2						1		1			1	1	1	1			3	7
Argentina	1950												1	1	1							1	2
	1956		1		1		1				1		1	1	1	1	1					2	7
Brazil	1950						1		1						1							0	3
	1956		1		1	1	1		1		1		1	1	1	1	1		1			3	9
Mexico	1950				1		1						1		1							0	4
	1956				1		1				1		1		1	1	1					1	6
South Africa	1950																					0	0
	1956								1							1	1					1	2
Philippines	1950														1							0	1
	1956										1		1		1	1	1		1			1	5
Australia	1950																1					0	1
	1956												1			1	1					1	2
Chile	1950																					0	0
	1956															1	1					1	1
India	1950																					0	0
	1956				1											1	1					1	2
Japan	1950																					0	0
	1956			1	1						1							1	1			2	3
France	1950																					0	0
	1956		1															1				1	1
Colombia	1950														1							0	1
	1956						1		1				1		1							0	4
Peru	1950														1							0	1
	1956						1		1						1							0	3
Uruguay	1950														1							0	1
	1956										1				1							0	2
Cuba	1950														1							0	1
	1956														1		1					0	2

Turkey	1950	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0
	1956	-	1	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	0	2
Italy	1950	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0
	1956	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	0	2
Belgium	1950	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0
	1956	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1	-	1	-	-	0	3
Israel	1950	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0
	1956	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	0	1
Panama	1950	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0
	1956	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	0	1
Netherlands	1950	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0
	1956	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	0	1
Total by company	1950	0	1	0	2	1	4	0	1	0	1	1	4	1	9	1	3	0	0	0	0	4	25
	1956	0	7	3	8	1	7	0	5	0	10	1	9	2	10	9	13	3	7	0	1	19	77

[1] Squibb in 1950, Olin Mathieson in 1956.

Source: FTC data request, 1957.

Parke, Davis led other manufacturers in 1956 in numbers of foreign antibiotics installations reported, with 9 manufacturing plants and 13 processing and packaging facilities outside the United States. American Cyanamid reported 3 manufacturing and 7 packaging facilities abroad; Pfizer reported 3 manufacturing and 7 packaging facilities; Olin Mathieson reported 2 manufacturing and 10 foreign packaging plants; Merck reported 1 plant equipped for manufacturing and 9 for packaging; and American Home Products reported 1 manufacturing and 7 packaging plants.

Table 22 also shows the number of new facilities added during the period between 1950 and 1956, and the type of facility in each country. Some of the antibiotics facilities listed are of substantial proportions. For instance, a plant recently constructed by Pfizer in England for the manufacture of oxytetracycline (but not packaging, which is done in another city) occupies 120,000 square feet of building space on an 80-acre site and was built at a cost of $7 million.[17] The Lilly plant in Mexico City contains 62,000 square feet of floor space.[18] The American Home Products plant in Mexico City occupies 35,000 square feet of floor space,[19] according to a 1951 report of the company. Merck reports building new plant facilities on a 200-acre site in Canada.[20]

Plant Expansion and Improvement

While the number of domestic manufacturing plants has remained fairly constant since the industry first began the production of penicillin during World War II, little similarity can be found between the small facilities of that period and the 19 extensive production plants now in operation.

Present-day plants are elaborately equipped with automatic devices to insure sterility, to test and measure each process; to agitate, cool, and ventilate the antibiotics mixtures; and finally, to filter, dry, and store each gram of antibiotics in a completely sterile environment. Provision must be made for huge fermentation installations, and for burial or other disposal of thousands of gallons of waste material. Provision must also be made for power, heat, filtered air and refrigeration, and for an immense water supply. Explosive chemicals used in the manufacturing process must be safely stored. Large numbers of animals are often maintained at the manufacturing site for use in connection with pharmacological testing of antibiotics products.

Expenditures for plant and equipment are required both to construct new capacity and to replace worn-out or outmoded facilities.

[17] "New Antibiotics Fermentation Plant," Chemistry & Engineering, London, October 22, 1955, p. 1378.

[18] Lilly report (6 months), 1956 (introductory letter).

[19] American Home Products annual report, 1951, p. 10.

[20] Merck annual reports, 1944 (introductory letter) and 1948, p. 6.

This industry has made rapid technological advances in the development of production units equipped with automatic controls which produce larger and more predictable yields of a better product. A result has been the outmoding of existing facilities and large expenditures to replace obsolete production facilities. For instance, the development of deep-vat fermentation outmoded all previous installations using flask fermentation, while perfection of techniques and the use of automatic devices and control equipment embodied in new and larger scale plants have progressively rendered the older and smaller deep-vat facilities obsolete. Then, too, the discovery of new antibiotics from time to time has stimulated expansions of total capacity to provide facilities to produce the newer ones while continuing the production of those already being marketed. Consequently, the capacity has increased substantially as a result of capital expenditures for both replacements and new production facilities, as the industry sought to attain greater volumes of production.

In order to trace the growth of the antibiotics industry capacity from 1943 to 1956, annual data on expenditures for new plants and equipment were gathered from the manufacturers. Companies known to have been engaged in antibiotics production at some time during the years from 1943 to 1956, inclusive, were asked to report their capital expenditures for domestic antibiotics plant and equipment during each calendar year of this period. When plants were used only in part for antibiotics operations, the companies were requested to include only the cost of the portions used in antibiotics operations. Replies from 19 companies indicate that their expenditures for new antibiotics plants during the period 1943 to 1956, inclusive, totaled approximately $270 million, and that more than half of this total was expended during the Korean action. This total represents gross plant expenditures and does not relate to book value of fixed assets at any particular time during the period.

Table 23 compares the annual expenditures reported by companies engaged in antibiotics manufacture at some time since 1943 with the total new plant and equipment expenditures of United States nondurable goods manufacturers as published in the 1957 Economic Report of the President.

Varying numbers of the 19 companies reported expenditures for plant and equipment in each of the 14 years, with no more than 15 reporting expenditures in any one year. It will be noted that the authorized expenditures during World War II (table 3) about equal the expenditures shown in table 23 for the first 4 years, 1943–46. During the Korean war years, the authorized expenditure (table 4) also approaches the expenditures listed in table 23 for the years 1951, 1952, and 1953.

TABLE 23.—*Expenditures for new plant and equipment: United States nondurable goods manufacturers and antibiotics manufacturers: 1943 to 1956*

Year	United States nondurable goods manufacturers		Antibiotics manufacturers		
	Millions of dollars	Percent change from preceding year	Millions of dollars	Percent change from preceding year	Number of companies
1943	n.a.		5.3		9
1944	n.a.		5.3	0	13
1945	2,390		5.6	+5.7	14
1946	3,680	+54.0	17.5	+212.5	15
1947	5,300	+44.0	18.0	+2.9	15
1948	5,650	+6.6	14.4	−20.0	14
1949	4,560	−19.3	16.3	+13.2	14
1950	4,360	−4.4	13.0	−20.3	14
1951	5,680	+30.3	49.5	+280.8	14
1952	6,020	+6.0	47.3	−4.4	14
1953	6,260	+4.0	53.9	+14.0	14
1954	5,950	−5.0	12.7	−76.4	12
1955	6,000	+0.8	4.9	−61.4	12
1956	7,360	+22.7	6.3	+28.6	12
Total			270.0		

n.a.—Not available.

Source: Economic Report of the President, January 1957, table F-28k, p. 154, for United States nondurable goods manufacturers, and FTC data request, 1957. schedule VII, for antibiotics manufacturers.

While the year-to-year changes, shown in table 23, are greater in the antibiotics industry than in total nondurable goods industries, similarity to a certain extent is to be noted in the fact that both the nondurable goods industry and the antibiotics industry show two periods of accelerated plant investment, the first occurring after the close of World War II, and the second during the Korean action. Also, both show periods when the amounts of annual investments fell off as compared with previous years.

Annual expenditures by antibiotics manufacturers are higher relative to sales than is to be found for nondurable goods manufacturers as a whole. For the 7-year period 1950 to 1956, expenditures on new plant averaged 4 percent of sales for nondurable goods manufacturers. Antibiotics manufacturers, on the other hand, spent an average of 9 percent of sales on new plant during this period (table 24). However, since this period included the unusual expansion occurring during the Korean action, it cannot be taken as a normal peacetime pattern. Some other individual nondurable industries, whose products like antibiotics were considered defense related during war and were in increasing demand during peace, may have had ratios as high as 9 percent.

American Cynanamid (Lederle) and Pfizer have invested most heavily in new domestic plant throughout the 14-year period, total gross expenditure amounting to around $50 million for each. Eli Lilly ranks third with an expenditure of nearly $40 million followed by Olin Mathieson (Squibb) and Bristol.

TABLE 24.—*Expenditure on new plant and equipment as a percentage of sales for nondurable goods manufacturers and antibiotics manufacturers: 1950 to 1956*

Year	All nondurable goods manufacturers			Antibiotics manufacturers		
	Millions of dollars		Percent of sales	Millions of dollars		Percent of sales
	Sales [1]	Expenditure on new plant and equipment [2]		Sales [3]	Expenditure on new plant and equipment [3]	
1950	126,000	4,360	3.5	249.2	13.0	5.2
1951	142,800	5,680	4.0	344.1	49.5	14.3
1952	142,800	6,020	4.2	289.1	47.3	16.4
1953	148,800	6,260	4.2	270.4	53.9	19.9
1954	147,600	5,950	4.0	287.9	12.7	4.4
1955	159,600	6,000	3.8	304.1	4.9	1.6
1956	166,800	7,360	4.4	337.7	6.3	1.9
1950–56 average			4.0			9.0

[1] Economic Report of the President, 1957, table E–33, p. 159, from Department of Commerce.
[2] Economic Report of the President, 1957, table E–28, p. 154, from Securities and Exchange Commission and Department of Commerce.
[3] FTC data requests, 1956 and 1957

Initially, antibiotics plant expansion was required to produce penicillin, streptomycin, and dihydrostreptomycin for civilian consumption after World War II restrictions on both civilian use of antibiotics and materials for plant construction were lifted (see table 23). Expenditures for new domestic plant and equipment did not drop markedly until after the conclusion of the defense expansion program in 1953.

Relation of Employment to Production

Total employment in the antibiotics industry, as estimated from the returns provided by the companies [21] and other information, probably did not exceed 35,000 in 1956.

Detailed employment data for their antibiotics operations were provided by 4 companies for 1950–56 and by another for 1953–56. The five companies are American Cyanamid, American Home Products, Bristol-Myers, Pfizer, and Upjohn.[22]

Between 1950 and 1956, the increase in employment of the 4 companies was 22.8 percent. The biggest gain, 73.2 percent, was in research and development. Other increases were 32.4 percent for detail men; 28.9 percent for employees in "all other" work, including administration, maintenance, service, transportation, and miscellaneous occupations; and 28.3 percent for employees in manufacturing operations. There was a decrease, amounting to 22.3 percent, in number employed in compounding and packaging.[23]

[21] FTC data request, 1957, schedule X.
[22] FTC data request, 1957.
[23] Data for the four companies are given in the form of percentage changes only to avoid disclosure of individual company data.

The antibiotics output of these 4 companies, measured in pounds, increased by 301.4 percent between 1950 and 1956. The average pounds produced per manufacturing worker increased by 212.7 percent, and the average pounds produced per packaging worker by 203.2 percent. There were apparently two main factors behind this sharp increase in productivity per worker. One was the increased production of nonmedicinal grades, which are handled efficiently in large bulk and without certain finishing operations applied to the medicinal grades. Production of nonmedicinal grades commenced in 1950, but was only 4 percent of total output in that year as against 28 percent in 1956 (see table 9). The second major factor behind increased productivity was increased automation and mechanization in both manufacturing and packaging, but particularly in the latter.

Total antibiotics employment of the 5 companies amounted to 16,997 in 1956, or approximately half of the estimated employment of the whole industry (see table 25). Research and development accounted for 8.4 percent of these employees; manufacturing, for 20.4 percent; compounding and packaging, for 14.1 percent; detailing, for 19.1 percent; and the "all other" category, for 38.0 percent.

Between 1953 and 1956, research and development employees of these 5 companies had increased by 22.9 percent; employment of detail men, by 17.9 percent; "all other" employment, by 12.9 percent; and manufacturing employment by 10.9 percent; while employment in compounding and packaging had decreased by 2.1 percent.

TABLE 25.—*Classifications of employees in the antibiotics industry, and the number and percent of each category to total employment—5 companies: 1953 and 1956* [1]

Classification	1953		1956	
	Number employed	Percent to total	Number employed	Percent to total
Research and development	1,159	7.6	1,424	8.4
Manufacturing	3,121	20.5	3,460	20.4
Compounding and packaging	2,452	16.1	2,401	14.1
Detail men	2,753	18.1	3,245	19.1
All other	5,727	37.7	6,467	38.0
Total	15,212	100.0	16,997	100.0

[1] Based on the usable returns of 5 companies including the 2 major producers.

Source: FTC data request, 1957.

Pounds of antibiotics produced per manufacturing worker of the five companies increased by 16.2 percent between 1953 and 1956, and pounds per packaging worker increased by 31.6 percent (see table 26). In other words, the 1953–56 advance in productivity per worker

of the five companies was significant, but was much less than the 1950–56 advance in productivity per worker of the four companies discussed previously.

TABLE 26.—*Antibiotics manufacturing and packaging employment and output—5 companies: 1953 and 1956*

Item	1953	1956	Percentage change from 1953 to 1956
Manufacturing workers (number)	3, 121	3, 460	+10. 9
Packaging workers (number)	2, 753	2, 401	−12. 8
Antibiotic output (pounds)	1, 352, 051	1, 740, 062	+28. 7
Average pounds per manufacturing worker	433	503	+16. 2
Average pounds for packaging worker	551	725	+31. 6

Source: FTC data requests, 1956 and 1957.

Research and Development Policies

If a manufacturer is to keep up with the progress of the industry, he must develop new products as well as new uses for old products. Trademarks and patents play an important role in new product identification and control.

From 1949 through 1956, 29 new antibiotics substances were produced commercially, although all of them did not remain in production. The industry so far has been successful in marketing new products more rapidly than old ones are abandoned, as shown in chart 1. During the span of years from 1948 through 1956, 17 penicillins and 22 other antibiotic substances were manufactured. In 1956, 4 new penicillin specialties were manufactured as well as 4 other new basic substances, which is the largest number of new products to be introduced in a single year. The distribution of innovations as between penicillins and other antibiotics, the number dropped out of production since they were first produced, and the number remaining in production in 1956 are shown in table 27. Tables 15 and 19 (previously discussed), listing the antibiotics manufacturers and the number of different kinds of antibiotics manufactured in 1948 and in 1956, show that most of the companies were producing more kinds in 1956 than in 1948, with the greatest expansion being in the new antibiotics other than penicillins.

The manufacturer leading in the development of new antibiotics is Pfizer, which produced 10 different substances in 1956; 9 besides the penicillins. This compares with only 3 basic substances produced in 1948. Merck produced 7 antibiotics in 1956 compared with 2 in 1948. Olin Mathieson produced 5 in 1956 as compared with 2 in 1948. Other manufacturers also developed new substances during the period.

TABLE 27.—*Number of new antibiotics introduced since 1948 and number produced in 1956*

Year	Penicillins			Other antibiotics			Total penicillins and others		
	Developed	Production dropped before 1956	Produced in 1956	Developed	Production dropped before 1956	Produced in 1956	Developed	Production dropped before 1956	Produced in 1956
1949	2	1	1	1	0	1	3	1	2
1950	0	0	0	2	0	2	2	0	2
1951	4	3	1	2	0	2	6	3	3
1952	0	0	0	3	2	1	3	2	1
1953	1	0	1	2	1	1	3	1	2
1954	0	0	0	1	0	1	1	0	1
1955	1	0	1	2	1	1	3	1	2
1956	4	0	4	4	0	4	8	0	8
Total	12	4	8	17	4	13	29	8	21

NOTE.—Actually, 29 items were produced in 1956; 21 of them were developed after 1948. See Chart 1 on p. 69.

Source: FTC data requests, 1956–57.

Innovations in the antibiotics industry are usually discovered, patented, and marketed on an individual company basis. All the new antibiotics appearing in 1949, 1950, and 1953 were 1-company "exclusives"; in 1951, 4 of the 6 new items were 1-company specialities; 2 of the 3 new items of 1952 are in this category; the single new product in 1954 is manufactured by only 1 company; 2 of the 3 new 1955 products are likewise 1-company items. Of the 8 new antibiotics produced in 1956, 7 are 1-company specialties. Sometimes, however, a product patented by one company is manufactured and sold by other companies under a licensing agreement. Table 16 shows that in 1956 patents were not held by the manufacturer on 8 of the 17 one-company products and that production was carried on under license in cases where patents are involved. Tetracycline is produced by three manufacturers, although one company, Pfizer, is the owner of the product patent. Pfizer has licensed Cyanamid and Bristol to manufacture this product. Pfizer also authorized Upjohn and Olin Mathieson to sell, but not to manufacture this antibiotic, which both companies purchase in bulk from Bristol. Each of these five companies sells tetracycline under its own trademark.[24] The details of the five-company arrangement are discussed in a later chapter of this report.

Table 20 (previously discussed) shows which antibiotics accounted for most of each company's revenue from its own production in 2 years: 1950 and 1956. The most important revenue earners of 1950 were in many cases of little importance by 1956. A number of the items on which companies relied for their principal revenue in 1956

[24] Pfizer markets tetracycline under the trademark "Tetracyn"; Cyanamid's trademark for the product is "Achromycin"; Bristol's is "Polycycline"; Olin Mathieson's (Squibb) is "Steclin"; and Upjohn's is "Panmycin."

were not known in 1950. Examples of new products not marketed in 1950 but of importance in 1956 are erythromycin, tetracycline, penicillin benzathine, penicillin "V," neomycin, and novobiocin. Table 20 also shows that 8 of the 12 antibiotics manufacturers changed to new leading products during the short span of 7 years. Of the remaining 4 companies, which kept the same products as leaders over the period, 2 (Abbott and Commercial Solvents) reported lower sales from their own production in 1956 than in 1950. The other 2 (Parke, Davis and Pfizer) continued, through the 7-year span, to show rising sales. Obviously, these shifts are the results of as well as the cause of a high degree of research activity, and furthermore, they are indicative of the high risks that much be borne in developing, producing, and marketing antibiotics, and the short period in which costs can be recovered.

New products have been a constant feature of the drug manufacturing industry for many years. Merck noted in 1947 that "Approximately 60 percent of sales for the year were of products which had been introduced in the last 12 years." [25] In 1948, it stated, "In general, the profit margin realized on new product groups is higher than older groups." [26] And in 1953, it stated "Profit margins are generally somewhat higher on newly introduced products than on older products." [27] Lilly stated in 1956 that 35 percent of its sales come from items introduced in the last 5 years.[28]

American Cyanamid said in 1949, "The higher margin of profit on pharmaceutical and biological products since January 1, 1946, resulted in part from the introduction of several new products." [29] (Aureomycin was introduced in 1948—one of the first broad spectrum antibiotics to be marketed.) Pfizer attributed its record sales in 1950 to the introduction of new products when it reported to stockholders. "The record sales of the year * * * were attributable to an almost immediate acceptance of several new products." [30] (Terramycin was first sold by Pfizer in 1950.) Bristol-Myers stated, "Perhaps the most fascinating research activity of this company is the search for new antibiotics." [31] Bristol stated in 1955 that 40 percent of sales were from new products,[32] and in 1956 this company claimed that 60 percent of its income comes from products developed in the past 10 years.[33] (Bristol-Myers began manufacturing its brand of tetracyline in 1954.)

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[25] Merck annual report, 1947, p. 3.
[26] Merck prospectus of April 19, 1949, p. 4.
[27] Merck proxy statement, April 30, 1953, p. 9.
[28] Lilly annual report, 1956.
[29] American Cyanamid prospectus, June 23, 1949, p. 8.
[30] Pfizer annual report, 1950, p. 3.
[31] Bristol-Myers annual report, 1951, p. 23.
[32] Bristol Myers annual report, 1955, p. 3.
[33] Bristol-Myers annual report, 1956, p. 4.

CHAPTER IV

The Production Process

Certain strains of micro-organisms are able to kill or repress the growth of other micro-organisms which cause diseases.[1] Science and industry have exploited this characteristic of these strains of micro-organisms and the result is today's antibiotic drugs. Each commercially produced antibiotic has prey against which it is often victorious, but there is no absolute rule. Sometimes one antibiotic will succeed where another has failed, even when both are usually successful against the specific disease-producing micro-organism.

Antibiotics are subjected to standards of potency and purity, but once they enter the chemical system of a human or animal, especially when the body has been invaded by one or more disease-causing micro-organisms, the result is not completely predictable.

The production process, starting with a selected strain of a particular micro-organism, constantly undergoes experimentation and change. In the following description, generalizations will be made, but, as the literature on production methods reveals, the micro-organisms are likely to supply surprises to manufacturers from time to time.

Antibiotics are produced principally by fermentation.[2] The fermentation process, which is essentially the same for all antibiotics as well as for certain hormones and vitamins, is more than a brewing process. It is controlled chemistry of a highly technical nature in which enzyme-catalyzed reactions yield the desired product. Micro-organisms produce the catalysts.[3]

This is what makes the production of antibiotics by fermentation a special process—it employs as catalysts enzymes produced by growing organisms instead of chemicals. The catalysts responsible for particular reactions of synthesis in antibiotics fermentation and the

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[1] This is accomplished by some fundamental disruption of metabolic processes, but just how it is done is unknown. Louis S. Goodman and Alfred Gilman, The Pharmacological Basis of Therapeutics, the Macmillan Co., New York, 1956, p. 1337.

[2] Chloramphenicol and tetracycline are partial exceptions. Most of today's commercial output of chloramphenicol is by chemical synthesis and some of the current output of tetracycline is by dechlorination of chlortetracycline which in turn is produced by fermentation. While the chemical synthesis of a penicillin has been achieved in a laboratory, commercial production is expected to continue to be by fermentation. Drug Topics, vol. 101, No. 7, April 1, 1957, p. 30; Chemical Week, vol. 80, No. 12, March 1957, p. 65.

[3] Elmer L. Gaden, Jr., "Fermentation Kinetics and Productivity," Chemistry & Industry, London: February 12, 1955, p. 165.

factors governing their formation in growing organisms are generally unknown.[4]

The essential features involved in the month-long process of producing an antibiotic substance will be covered briefly in the following order:[5]

1. The micro-organism.
2. The medium.
3. Sterilization and aseptic techniques.
4. The fermentation process.
5. Recovery of fermentation products.
6. Disposal of fermentation wastes.

Manufacturers develop their own cultures, formulas for the medium, and special equipment in an effort to improve production yields and the stability of the product. But the essential steps in the major stages of production are strikingly similar among the many antibiotics. Once the fermentation process has been completed, however, there are notable variations in methods necessary for recovering and purifying different antibiotics from fermentation broths.

The first step to be taken before the antibiotic production process can be commenced is to find an efficient antibiotic strain. This means finding a strain of micro-organism capable of producing an effective, relatively nontoxic antibiotic substance in commercial quantities.

The Micro-organism

Search for effective strains

Effective strains of micro-organisms for production of antibiotic medicines must be searched out, and after they are found, preserved. In order to find these useful micro-organisms, a large number of widely sampled soils, grain, and foodstuffs are screened, and certain cultures are selectively isolated. From among the selected cultures, a few superior producing micro-organisms are chosen.

These micro-organisms may be further improved by natural selection or by a series of treatments with X-rays, heat neutron bombardment, ultraviolet light, or by the action of such chemical agents as nitrogen mustard and colchicine.[6]

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[4] W. E. Brown, "Penicillin," Encyclopedia of Chemical Technology, vol. 9, The Interscience Encyclopedia, Inc., New York: 1952, p. 933.

Elmer Gaden, Jr., "Fermentation," Chemical Engineering, vol. 63, No. 4, April 1956, p. 160.

[5] Samuel C. Beesch and G. M. Shull, "Fermentation," Industrial & Engineering Chemistry, vol. 47, No. 9, pt. II, September 1955, p. 1868.

[6] W. E. Brown, "Penicillin," Encyclopedia of Chemical Technology, vol. 9, The Interscience Encyclopedia Inc., New York: 1952, p. 928.

W. B. Emery, "Bacteriological Problems in Translating from Small Equipment to the Industrial Scale," Chemistry & Industry, London: March 5, 1955, p. 240.

Beesch and Shull, "Fermentation," Industrial & Engineering Chemistry, vol. 47, No. 9, September 1955, p. 1868.

The sources of present successful antibiotics are principally within two groups of micro-organisms found in the soil; namely, molds and bacterial streptomyces. From the molds come the penicillins, including penicillin G, the basic penicillin substance, penicillin V, and other minor substances not widely sold. From the streptomyces come the streptomycins, the tetracyclines, chloramphenicol, neomycin, erythromycin, carbomycin, viomycin, nystatin, oleandomycin, cycloserine, and novobiocin (vitamin B_{12} also may be produced from the genus streptomyces).[7] From another soil bacterial organism comes polymyxin. Within these groups of micro-organisms, only a few selected strains have survived all the tests.

One successful antibiotic, bacitracin, had a quite different origin. From the wound of a patient named Tracy, a strain of *Bacillus subtilis* was isolated which produced an antibiotic, and, in honor of the patient, was named "*B. subtilis* Tracy I." The antibiotic was ultimately named "bacitracin."[8]

Penicillin was originally produced from a strain of *Penicillium notatum*, but this strain was later replaced by *Penicillium chrysogenum*, which gave higher yields. This organism could be grown under the submerged-culture technique that in 1944 began to replace the surface-culture method of production which had employed many small flasks or bottles. Later an X-ray mutant of *P. chrysogenum* was found which gave higher yields than the original strain; finally, an ultraviolet mutant of this latter strain, called *P. chrysogenum* Q176, giving a minimum yield of 2,000 units of penicillin per milliliter of fermentation broth, was developed. This is the strain now employed for the production of benzylpenicillin (penicillin G), the basic penicillin salt in general use.[9] Although benzylpenicillin was reported to have been chemically synthesized in the laboratory at Cornell University in 1946,[10] commercial production has always been by fermentation.

A recent development in penicillin involves the use of the initial culture strain, *P. notatum*, for production of a product, phenoxy-

[7] Selman A. Waksman and H. A. Lechevalier, "Streptomyces Antibiotics," Encyclopedia of Chemical Technology, vol. 12, The Interscience Encyclopedia, Inc., New York: 1954, pp. 57 and 72.

H. B. Woodruff, "Microorganisms," Encyclopedia of Chemical Technology, vol. 9, pp. 85–96.

Antibiotics Annual 1956–57, Medical Encyclopedia, New York: 1957, pp. 228, 1031.

J. A. Kiser and H. B. Woodruff, "Antibiotics," Encyclopedia of Chemical Technology, vol. 2, p. 7 ff.

[8] Ernest Jawetz, "Polymyxin, Neomycin, Bacitracin," Medical Encyclopedia, Inc., New York: 1956, p. 50.

[9] W. B. Woodruff, "Microorganisms," Encyclopedia of Chemical Technology, vol. 9, The Interscience Encyclopedia, New York: 1952, p. 95.

W. E. Brown, "Penicillin," Encyclopedia of Chemical Technology, vol. 9, The Interscience Technology, 1952, p. 929.

[10] Hans T. Clarke, John R. Johnson, Sir Robert Robinson, editors, The Chemistry of Penicillin, Princeton University Press, Princeton, N. J., 1940, p. 9, n. 9.

methyl penicillin, commonly called penicillin V.[11] This is the penicillin form that was recently produced synthetically in a laboratory experiment at the Massachusetts Institute of Technology.[12]

Penicillin V is the exception; other penicillin salts are produced from the *P. chrysogenum* Q176 strain and achieve their separate identities only during or after the fermentation cycle.

Once a high-producing strain has been selected, it must be maintained so that the organism remains viable and capable of producing the antibiotic at a constant high level. For this purpose the chosen culture is usually freeze dried; it may be maintained in this state for months.[13] The freeze-dried culture is usually stored in small ampoules in a sterile bank or room.[14]

Along with the improvement of strains there has been a search for new antibiotics—new strains that will do a better or different job than those antibiotics already in use. Because of the intensity of this search, a new antibiotic is occasionally unearthed and a new product marketed, but only after prolonged research at all levels—medical, developmental, and production. Between 3,000 and 4,000 antibiotic strains have been identified,[15] but less than two a year on the average have survived pharmacological and clinical testing, and thus could be marketed as antibiotic products.

Controlled growth of selected strains

Commercial production of an antibiotic starts when spores from a master culture are taken through several stages of successively increasing volume by feeding on increasing quantities of a suitable nutrient or food base.

The spores, which are "awakened" when the ampoules are opened in a sterile room, are transferred—under continued sterile conditions—to a small container in which the first stage of encouraged multiplication takes place.[16] The encouragement consists of a favorable temperature, a supply of oxygen (the inoculum is aerated by continuous shaking in a bottle or flask), and the proper nutrition.[17]

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[11] Business Week, March 23, 1957, p. 124.

[12] Drug Topics, vol. 101, No. 7, April 1, 1957, p. 30; Chemical Week, vol. 80, No. 12, March 1957, p. 65.

[13] W. B. Woodruff, "Microorganisms," Encyclopedia of Chemical Technology, vol. 9, The Interscience Encyclopedia, New York: 1952, p. 106.

W. E. Brown, "Penicillin," Encyclopedia of Chemical Technology, vol. 9, The Interscience Encyclopedia, New York: 1952, p. 929.

[14] "New Antibiotics Fermentation Plant," Chemistry & Industry, London: October 22, 1955, p. 1378.

Samuel C. Beesch and G. M. Shull, "Fermentation," Industrial & Engineering Chemistry, vol. 47, No. 9, p. 1868.

[15] Henry Welch, "Antibiotics: A Discussion of Recent Developments, Use and Side Effects," International Record of Medicine, vol. 168, No. 7, July 1955, p. 450.

[16] "New Antibiotics Fermentation Plant," Chemistry & Industry, London: October 22, 1955, p. 1378.

[17] W. E. Brown, "Penicillin," Encyclopedia of Chemical Technology, vol. 9, The Interscience Encyclopedia, New York: 1952, pp. 929–930.

The first stages of spore development (for penicillin production) in a solid agar or grain usually require about 5 days. The spores thus obtained are suspended in sterile water and a specific quantity is used as inoculum for the first of several vegetative stages, each designed to give from 5 to 10 percent inoculum to the succeeding stage; that is, to give volume increase from tenfold to twentyfold at each stage.[18]

The number of inoculum stages necessary in industrial operations is dependent primarily on the working capacity of the production fermenter. (The working capacity is usually about three-fourths of the size of the fermenter.) Sufficient amounts of inoculum from the original spore source must be maintained at each plant. Usually, the time elapsing from the growth of the original freeze-dried spore source until sufficient inoculum is available for fermentation is about 2 weeks.[19]

The Medium

While the mold is being grown in several stages of increasing volume, the medium is being prepared for use in the big fermenters, usually 15,000 to 30,000 gallons in size.[20]

The medium is composed of nutrients necessary for production of the antibiotic substance. Water is added, the mixture is sterilized, and then pumped to the large fermenters. The mold is then added to the medium, and growth of the entire batch is speeded by agitation and aeration. Tanks are cooled during the final growth process by the circulation of hundreds of thousands of gallons of water. It is said that enough water is used daily by one antibiotics plant to supply 100,000 people.[21]

The content of the medium is important. In fact, an industrial fermentation process has been described simply as the correct combination of medium and micro-organism.[22]

The function of the medium in antibiotics production is to provide conditions for satisfactory large-scale growth and optimum activity of the micro-organism. Growth and catalytic activity must be satis-

[18] Ibid., p. 929.

[19] Ibid., pp. 929, 930.

W. B. Woodruff, "Microorganisms," ibid., p. 101 ff.

[20] "New Antibiotics Fermentation Plant," Chemistry & Industry, London: October 22, 1955, p. 1378; "Kentish Terramycin Plant," The Chemical Age, No. 1891, London: October 8, 1955, p. 773.

[21] "New Antibiotics Fermentation Plant," Chemistry & Industry, London, October 22, 1955, p. 1378; "Kentish Terramycin Plant," The Chemical Age, No. 1891, London: October 8, 1955, p. 773.

John E. McKeen, "Antibiotics Production Development," Drug & Cosmetics Industry, vol. 77, No. 2, August 1955, p. 184 ff.

[22] Samuel C. Beesch and G. M. Shull, "Fermentation," Industrial & Engineering Chemistry, vol. 47, No. 9, pt. II, September 1955, p. 1868.

factory from the point of view of the desired end product, and satisfactory from a commercial point of view; that is, the antibiotic yield must be high.[23]

Raw material for the medium is composed of nitrogen sources and carbohydrate energy sources [24] (see also table 29, p. 120). The basic medium used for penicillin production contains lactose, corn steep liquor, calcium carbonate, animal or vegetable oils, and salts.[25] There is no standard formula; each manufacturer develops its own medium [26] and apparently makes frequent changes in its own formula.

Corn steep liquor, one of the items usually used in the medium because it appears to boost the antibiotic yield, is purchased in considerable quantity from the corn wet-milling industry by the antibiotics manufacturing industry.[27] Most of the Nation's annual output of corn steep—estimated to range between 100 and 150 million pounds—is consumed in antibiotics manufacture.

Trace materials, which appear to function as catalysts, are sometimes added to the medium to increase the yield or rate of production of the antibiotic. In the production of chlortetracycline, iron, potassium, phosphate and magnesium are used as trace elements; in penicillin production nonmetal stimulatory substances are often added to the medium, such as ethylamine, alkaloids, and fatty acid esters.[28]

Certain precursors, when added to the medium, favor the increased yield of the desired antibiotic, and discourage the production of other substances during the fermentation process. In penicillin G production, phenylacetic acid is sometimes used as a precursor.[29]

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[23] Ibid., p. 1868.

[24] Carbohydrate or energy sources include molasses, glucose, starch, wood sugars, corn, wheat, milo, rye, and potatoes. Nitrogen sources used in various industrial fermentations of antibiotics include distillers' solubles, casein, whey, gluten, fish meal, protein hydrolyzates, meat scraps, ammonia or ammonium salts, grains of various types, corn steep liquor, peptones, tankage, soybeans, bean, peanut, linseed, and cotton seed meals; wheat bran, oat hulls and lentils. Samuel C. Beesch and G. M. Shull, "Fermentation," Industrial & Engineering Chemistry, vol. 47, No. 9, pt. II, September 1955, pp. 1868–1869.

W. E. Brown, "Penicillin," Encyclopedia of Chemical Technology, vol. 9, The Interscience Encyclopedia, Inc., New York; 1952, p. 1930.

[25] David Perlman, Arthur E. Tempel, Jr., and W. E. Brown, "Fermentation," Industrial & Engineering Chemistry, vol. 45, No. 9, September 1953, p. 1957.

See also input materials of two manufacturers for penicillin and dihydrostreptomycin shown in table 30, p. 122.

[26] Selman A. Waksman and H. A. Lachevalier, "Streptomyces Antibiotics," Encyclopedia of Chemical Technology, vol. 13, The Interscience Encyclopedia Inc., New York: 1954, p. 63.

[27] Chemical Week, pt. I, vol. 75, No. 12, September 18, 1954, p. 106.

[28] Samuel C. Beesch and G. M. Shull, "Fermentation," Industrial & Engineering Chemistry, vol. 47, No. 9, pt. II, September 1955, p. 1869.

[29] David Perlman and Charles L. Kroll, "Fermentation," Industrial & Engineering Chemistry, vol. 46, No. 9, September 1954, p. 1818.

W. E. Brown, "Penicillin," Encyclopedia of Chemical Technology, vol. 9, The Interscience Encyclopedia, Inc., New York: 1952, p. 931.

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When penicillin O is desired, allylmercaptoacetic acid is added.[30] For streptomycin, inositol and glycin have been used as precursors.[31]

Excessive foam must be prevented, and for this reason antifoaming agents such as lard oil are piped into the fermenters.[32]

Sterilization and Aseptic Techniques

Aseptic technique in industrial fermentation begins in the laboratory with the use of a pure culture of the antibiotic-producing mold. Utmost precaution is required throughout the laboratory and subsequent plant process to avoid the entrance of contaminating microorganisms. All media are heat sterilized to kill the organisms present in water or in the raw materials. In large-scale industrial processes, long heating periods under pressure are sometimes necessary to insure sterility. A temperature of about 250° F. for 20 to 60 minutes is quite common.[33]

The liquid is agitated for thorough mixing to prevent unwanted micro-organisms from surviving in a cool area; one such organism could be a source of contamination of the whole batch. At the same time, care must be taken that nutritional qualities of the medium are not damaged by overheating.

Sterility requirements impose restrictions on the use of some materials in the medium. Moist bran, for instance, is not a practical ingredient for the medium because of the difficulty of sterilizing it. Difficulties are also encountered when potato, dilute gelatin, or some sugars are subjected to pressure sterilization.[34] All equipment must also be maintained under sterile conditions.

The success of antibiotics production depends on avoidance of contamination by unwanted organisms. Such contamination can result in the destruction of the desired antibiotic substance and the growth instead of foreign organisms. For this reason, frequent tests are made throughout the process to insure that a foreign organism has not "taken over."

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[30] Louis S. Goodman and Alfred Gilman, The Pharmacological Basis of Therapeutics, The Macmillan Co., New York: 1956, p. 1328.

David Perlman and Charles L. Kroll, "Fermentation," Industrial & Engineering Chemistry, vol. 46, No. 9, September 1954, p. 1813, citing J. H. Ford, Antibiotics and Chemotherapy 3, 1149 (1953).

[31] W. E. Brown, "Penicillin," Encyclopedia of Chemical Technology, vol. 9, The Interscience Encyclopedia, Inc., New York: 1952, p. 922.

[32] Ibid., p. 933.

[33] At the boiling points (212° F.) for atmospheric pressure, 108 minutes are needed, while at 290° F. sterilization is accomplished in 2.5 minutes. Elmer Gaden, Jr., "Fermentation," Chemical Engineering, vol. 63, No. 4, April 1950, p. 164.

[34] H. B. Woodruff, "Microorganisms," Encyclopedia of Chemical Technology, The Interscience Encyclopedia, Inc., New York: 1952, p. 102.

The Fermentation Process

The batch method of fermentation, rather than the continuous method, is used in the production of antibiotics.[35] This method is necessary because of the continuing problems of culture stability and contamination in antibiotics fermentation. The advantage in the batch method is that contamination, when it occurs, may be limited to a single fermenter without involving the entire system. If the problem of contamination cannot be solved, the batch is thrown out and the source of contamination found before production of the antibiotics substance is resumed.

As shown in table 29 (p. 120), the duration of the fermentation period varies among the antibiotics products. Penicillin is shown as requiring an average fermentation time of 100 to 120 hours; streptomycin, from 60 to 80 hours; chloramphenicol, 72 hours; chlortetracycline, from 48 to 72 hours; and oxytetracycline, 48 hours. Another observer, relying on data from different plants than those relied upon in developing the figures shown in the table, states that penicillin requires a shorter fermentation period than streptomycin. The time periods shown in the table are not standard and vary between manufacturers of the same product, and, according to some observers, vary from batch to batch depending on the medium used or other changes in the production process. The fermentation cycle may be extended beyond the point of time of the maximum productivity of the microorganisms in order to achieve a more economic overall operation.[36]

During the course of fermentation, four major considerations must be kept paramount. They are aeration, temperature, pH of the medium,[37] and control of foam. Aeration and agitation are provided mechanically, and vary according to the product desired and the medium used. Cooling of the batch is necessary because of the heat released when carbohydrates in the medium are converted to carbon dioxide, and is provided by a flow of water over the surface of the fermenter or in coils or jackets.[38] The chief methods of pH control are by the use of buffers or by intermittent addition of alkalis or acids.

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[35] Beesch and Shull, "Fermentation," Industrial & Engineering Chemistry, vol. 47, No. 9, September 1955, pp. 1870–1871.

[36] Elmer Gaden, Jr., "Fermentation," Chemical Engineering, vol. 63, No. 4, April 1956, p. 173.

[37] pH refers to the degree of acidity or alkalinity of the solution.

[38] Samuel C. Beesch and G. M. Shull, "Fermentation," Industrial & Engineering Chemistry, vol. 47, No. 9, pt. II, September 1955, p. 1870.

Modern fermentation equipment is "amazingly standard."[39] The vessels are usually made of stainless steel. Sizes differ, but large manufacturers ordinarily employ ten to fifty 15,000- to 30,000-gallon vessels. Operating capacity is usually about 75 percent of total capacity. Agitation is provided by some type of turbine impeller mounted on a central shaft. Air is admitted through an external sterilizing filter, airpipe, and sparger. Control and recording devices used in the process include air pressure and flow recorder-controller, temperature (cooling water) recorder-controller, tank pressure recorder, and antifoam addition-controller. Any additions to the mixture, such as air or antifoam agents, must first be sterilized.

Two types of fermenters are used—the seed (inoculum) fermenter and the larger production fermenter. Table 28 gives the general requirements for fermentation equipment used in the manufacture of antibiotics as well as certain other fermentation products. There are some exceptions. The fermentation of yeast is done in a somewhat different vessel and solvent fermenters (ethanol, butanol, and acetone) are larger in size and do not require agitation and aeration.

The month-long antibiotics production process has reached a high degree of automation. While gages and recorders operate on an around-the-clock basis, one skilled technician can check readings in several buildings. Thus, much of the process of production (including fermentation) requires few employees in a modern antibiotics plant.

TABLE 28.—*Fermentation equipment*

Type	Uses	Operating capacity, gallon	Agitation	Aeration
Seed (inoculum) fermenters.	General; antibiotics, vitamins, organic acids.	50–1,500	Single or double, flat and curved blade turbines, 0.1 to 0.7 horsepower per 100 gallons.	Sparger rings or pipes 1–4 feet per minute superficial velocity.
Production fermenters.	General; antibiotics, vitamins, organic acids.	5,000–25,000	Multiple flat and curved blade turbines, 0.2–1 horsepower per 100 gallons.	Sparger rings or pipes 2–6 feet per minute superficial velocity.

Source: Elmer Gaden, Jr., "Fermentation," Chemical Engineering, vol. 63, No. 4, April 1956, table II, p. 169.

Recovery of Fermentation Products

The next step is to harvest the antibiotic product from the fermentation broth. At the end of the brewing cycle, thousands of gallons of

[39] The author's complete statement is, "Despite the extreme atmosphere of competitive secrecy which envelops the fermentation industry, particularly its pharmaceutical branch, equipment is amazingly standard. This stems in part from the fact that most major producers of antibiotics and related materials got their start under the more or less cooperative arrangements of the government's war-time penicillin program." Elmer Gaden, Jr., "Fermentation," Chemical Engineering, vol. 63, No. 4, April 1956, p. 159 ff.

broth contain only small amounts of the antibiotic substance. Recovery problems are due mainly to the low concentraction in which these chemicals are found and to the need to free a highly pure primary product from trace contaminants of structurally similar but biologically inactive or harmful entities.[39]

The quantity of an antibiotic yielded by a given fermentation batch is of great economic significance to the manufacturer. The higher the product concentration in terms of a given material input and of time spent and equipment used on a given quantity of the product, the higher the reward. The difference between a 1-gram- and a 5-gram-per-liter yield is the difference between whether a 10,000-gallon fermentation batch represents 37,850 grams or 189,250 grams of an antibiotic. It does not pay, however, to push the product concentration too high if it involves a disproportionate expense for either raw materials or processing.

Both potency and the techniques used to produce a certain potency or yield are carefully guarded by the manufacturers, except when it may be necessary to disclose a particular method in order to obtain a process patent. Yields, therefore, differ among the various plants, and to a smaller extent they differ in the same plant between one period of time and another. Most estimates of yields for particular antibiotic substances by chemical engineering experts are in the nature of "educated guesses."

Table 29 presents recently published estimates for broth yields of some antibiotic substances. The ranges shown for the yields of four principal products are as follows: penicillin, 1 to 3 grams per liter; streptomycin, 1.5 to 4 grams; chlortetracycline, 1.3 to 2.5 grams; and oxytetracycline, 1 to 5 grams.[40] One authority states his belief that the quoted figures are conservative, at least for penicillin and chlortetracycline, and that the maximum yields of penicillin are probably 4 grams per liter, and for streptomycin and both chlortetracycline and oxytetracycline are probably in the neighborhood of 4½ grams per liter.[41] It is pointed out that broth potencies of streptomycin and the broad spectrum antibiotics would be expected to fall in the same broad range, other factors being equal, since all are products of organisms of the *Streptomyces* group, while penicillin, produced from a different organism under different conditions, might have a different

[39] Elmer Gaden, Jr., "Biochemicals Processing," Chemical Engineering, vol. 64, No. 5, May 1957, p. 240.

[40] The author of this table states that "the data given are intended more for illustration and example than for completeness and accuracy of detail. Published information—particularly for antibiotic and other pharmaceutical processes—is rarely more than an approximation to the actual conditions employed and results obtained anyway." Elmer Gaden, Jr., "Fermentation," Chemical Engineering, vol. 63, No. 4, April 1956, p. 161.

[41] British and Canadian patents disclose a 5 gram per liter yield on Cyanamid's chlortetracycline.

TABLE 29.—*Summary of the commercial fermentation process (biosynthesis)*

Product	Raw materials	Enzyme-producing organism	Temperature C.	pH	Aeration	Time, hour	Product concentration, gm./liter
Riboflavin	Grain stillage, meals, glucose, salts, nitrogen supplements.	Eremothecium ashbyii or ashbya gossypii.	28–32	5.5–6.5	High	60–70	102.
Vitamin B12	Glucose, grain meals, nitrogen supplements, salts.	Streptomyces griseus or Streptomyces olivaceus.	26–30	6.5–7	do	60–70	0.3–0.6.
			28–30	7	do	65–120	1–3.
Penicillin G [1]	Lactose, glucose, corn steep liquor, salts, phenylacetic acid.	Penicillium chrysogenum	22–28	6–7	do	100–120	2–3 (1.5–2.0; 1–3).[2]
Streptomycin [1]	Glucose, soybean meal, nitrogen supplements, salts.	Streptomyces griseus	25–30	6.5–7	do	60–80	1.5–2.5 (4.0).[2]
Chloramphenicol [1]	Starch, glycerol, nitrogen supplements, salts.	Streptomyces venezuelae	27–28	6.5–7.5	do	72	0.3–0.5.
Chlortetracycline [1]	Sucrose, corn steep liquor, salts	Streptomyces aureofaciens	26–28	6.2	do	48–72	1.3–2.5.
Oxytetracycline [1]	Starch, soybean meal, salts	Streptomyces rimosus	24–30	7	do	48	1+(1–5).[2]
Bacitracin [1]	Glucose, sucrose, nitrogen supplement	Bacillus licheniformis	37	6–7	do	36–48	1.5.
Yeast	Molasses, nitrogen supplement or sulfite liquor, salts.	Saccharomyces cerevisiae	25–30	4–5	Very high	10–20	5.
		Torulopsis utilis	32–34	4.5–6	do	([3])	5–7.

[1] Antibiotics.
[2] Elmer Gaden, Jr., "Biochemicals Processing," Chemical Engineering, vol. 64, No. 5, May 1957, pp. 240–241.
[3] Continuous.

Source: Elmer Gaden, Jr., "Fermentation," Chemical Engineering, vol. 63, No. 4, April 1956, table I, p. 163.

range of product concentration, reported by some to be lower and by table 29 to be narrower than the range for streptomyces products.

In comparison with the 1956 range of yields shown in table 29, the president of Pfizer reported that in 1953 yields of antibiotics (without specifying the classes of antibiotics) were at the average rate of 1,600,000 pounds from 450 million gallons of broth (280 gallons per pound), or 0.4 gram per liter.[42]

Previously one company had reported that in 1945, 17,442 gallons of broth had to be processed to produce 1 pound of penicillin or 0.007 gram per liter of broth. Thus, yields of penicillin appear to have increased at least 142 times between 1945 and the time of Dr. Gaden's observations (from 0.007 gram per liter in 1945 to a minimum of 1.0 gram per liter in 1956).

It is understandable that intensive research continues to be carried on to improve yields. This research takes the form of searches for high-producing strains of micro-organisms and for improvements in the inoculum or medium, or some mechanical variation that will stimulate more growth of the antibiotic substance.

A recent article quotes Lederle (American Cyanamid) as stating that it now gets higher production from considerably less starting materials than ever before, "thanks to a particularly busy microbe strain that it's recently bred." In this way, production is boosted without expansion of physical plant.[43]

The first step in the recovery of antibiotics from the fermentation broth is to transfer the brew to a holding tank under strictly sterile conditions. Here mycelia and other solids are removed.[44] Chemicals are added to aid the precipitation out of solution of an intermediate salt of the antibiotic.[45] Penicillin, for instance, may be purified and extracted from the clear broth by a three-stage solvent extracting process with the use of a countercurrent solvent extractor. The penicillin may then be converted into various crystalline penicillin salts.[46]

For streptomycin, the medium is treated with acid to release the streptomycin bound to the cells of the micro-organism. The cells are removed by filtration, the filtrate is neutralized and passed over an exchange resin, the resin is treated with acid, and the released streptomycin salt is purified further and crystallized.[47] The filtrate can also be used as the basis for dihydrostreptomycin.

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[42] John E. McKeen, "Antibiotics Production Development," Drug & Cosmetic Industry, vol. 77, No. 2, August 1955, p. 184.

[43] "Tetracycline: Engineered to Market," Chemical Engineering, vol. 64, No. 3, March 1957, p. 228.

[44] W. E. Brown, "Penicillin," Encyclopedia of Chemical Technology, The Interscience Encyclopedia, Inc., New York: 1952, p. 1929, 934.

[45] "Antibiotics Production Plant," The Engineer, vol. 201, No. 5240, London: June 29, 1956, p. 779 ff.

[46] David Perlman, Arthur E. Tempel, Jr., and W. E. Brown, "Fermentation," Industrial & Engineering Chemistry, vol. 45, No. 9, September 1953, p. 1961.

[47] David Perlman and Charles L. Kroll, "Fermentation," Industrial & Engineering Chemistry, vol. 46, No. 9, September 1954, p. 1821.

No general principle can be laid down for the recovery of fermentation products. For the main product (not for recovery of a byproduct), however, the standard techniques of salt formation, distillation, adsorption and elution, and solvent extraction are commonly used.[48]

There is always some loss of the antibiotic in the process of harvesting it from the fermentation broth. The manufacturer's problem is to keep the loss to a minimum.

A general summarization of the requirements for fermentation and recovery of some of the antibiotics is presented in table 29 which appeared in a 1956 publication. Antibiotics are grouped under the biosynthesis process, along with riboflavin, vitamin B_{12}, and yeast.[49]

Data for conclusions regarding the relationship of yields to unit cost of different antibiotics are not available. A wide variety of chemicals and nutrients are used in the production, recovery, and purification of antibiotics; there is no standard formula for any particular product or for any particular manufacturer. Table 30 lists the major materials used by two manufacturers during the course of production of penicillin and dihydrostreptomycin in 1952, disclosing the variety of major input requirements used in the course of producing these two standard substances.

TABLE 30.—*Principal raw materials required for production of 25,000 pounds of 2 antibiotics*

Penicillin			Dihydrostreptomycin		
Calcium carbonate	lbs	172,380	Cerelose	lbs	1,148,875
Lard oil	do	677,700	Soybean meal	do	891,800
Phenylacetamide	do	180,000	Corn steep solids	do	255,938
Corn steep liquor	do	2,257,450	Sodium chloride	do	129,675
Formaldehyde	do	62,000	Calcium chloride	do	51,188
Dextrine tailings	do	1,161,360	Oxalic acid		125,125
Sulfuric acid	do	255,672	Hydrochloric acid	do	312,813
Sodium sulfate	do	15,144	Hyflosupercel	do	1,228,500
Pentacetate	do	314,930	Sodium hydroxide	do	1,097,688
Soda ash	do	106,080	Citric acid	do	48,913
Sodium phosphate	do	74,000	Triethylamine	do	71,435
Potassium acetate	do	11,760	Soda ash	do	19,565
			Sulfuric acid, CP	do	316,225
			Hydrochloric acid, CP	do	298,025
			Methanol	gallons	243,425
			Boric acid	lbs	182,910

Source: Applications for certificates of necessity filed by 2 manufacturers in 1952.

Disposal of Fermentation Wastes

The thousands of gallons of broth, from which antibiotics are recovered, become a waste disposal problem. This broth contains mycelia, remnants of the nutrients used, and small quantities of the antibiotic. The vitamin B_{12} content of the residue from streptomyces

[48] Elmer Gaden, Jr., "Biochemicals Processing," Chemical Engineering, vol. 64, No. 5, May 1957, p. 237 ff.

Samuel C. Beesch and G. M. Shull, "Fermentation," Industrial & Engineering Chemistry, vol. 47, No. 9, September 1955, p. 1872.

[49] Elmer Gaden, Jr., "Fermentation," Chemical Engineering, vol. 63, No. 4, April 1956, p. 163 ff.

fermentation is sometimes recovered and used in animal feed supplements. Sometimes the mycelium is dried and sold, but more often, provision for disposal must be made.

The broth cannot be dumped into a river because of the damage to aquatic life and the offensive odor of decomposing organic matter. The volume is too great for most sewage systems. One satisfactory waste disposal method is by trickling filters. This is reportedly less expensive than evaporation and incineration.[50] A Pfizer plant is so located that waste broth can be piped into the ocean, but this is an exceptional advantage not enjoyed by most manufacturers. Provision for burial of fermentation wastes is probably the general rule in the antibiotics industry, necessitating large areas of land adjacent to plant sites.

Further Processing of Bulk Antibiotics

After a pure crystalline antibiotic has been produced and stored in a sterile container, it may be further processed by the manufacturer, or sold in bulk to other processors, for finishing into medicines, feed supplements, crop sprays, food preservatives, or other possible products.[51] The handling of antibiotics, once the pure bulk material has been produced, is similar to the handling of other drugs and medicines, and need not be described in detail.

Certification by the Food and Drug Administration

Antibiotics for medicinal use, like other drugs, are prepared in two major forms. One form is for injection and the other for oral administration.

Purity and potency tests are made of the antibiotic output of each fermentation batch. With certain exceptions, samples of each batch are sent to Washington representatives of the companies who turn the samples over to the Food and Drug Administration for checking and certification of the batch. Batch certification is for potency and purity. Likewise, sample dosage forms are submitted by the processor to the Food and Drug Administration for certification of labeled potency and other tests. For tablets and capsules, potency and moisture tests are conducted. For injectable forms, tests for sterility, pyrogens (fever-producing material), toxicity, moisture and pH are conducted.[52]

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[50] Samuel C. Beesch and G. M. Shull, "Fermentation," Industrial & Engineering Chemistry, vol. 47, No. 9, September 1955, p. 1872.

David Perlman, Arthur E. Tempel, Jr., and W. E. Brown, "Fermentation," Industrial & Engineering Chemistry, vol. 45, No. 9, September 1953, pp. 1961, 1962.

[51] Only chlortetracycline and oxytetracycline have been approved by the Food and Drug Administration for use as a food preservative. This use is limited to dipping of dressed poultry. No approval has been given for use of any antibiotic as a fish preservative. The Food and Drug Administration has approved the use of antibiotics as crop sprays so long as no residue remains on the food—when it does it is regarded as contamination by the Food and Drug Administration.

[52] The antibiotics required to be certified under section 507 of the Federal Food, Drug, and Cosmetic Act are penicillin (except crystalline forms of sodium and potassium penicillin when not combined with an antibiotic requiring certification), streptomycin, dihydrostreptomycin, chloramphenicol, tetracycline, chlortetracycline, and bacitracin.

Before a new antibiotic substance can be marketed, it must be submitted to the Food and Drug Administration with a complete dossier covering all clinical and pharmacological tests which have been made by the manufacturer. When Food and Drug approves a substance it also establishes the period of stability of the antibiotic and requires that the product be dated to show the length of time of full potency. As products have been improved, stability periods have increased and, upon application by the manufacturers supported by proof, the Food and Drug has from time to time extended the "expiration date" of the product. Many items have now proved to be stable for as long as 5 years at room temperature, which is in sharp contrast to the situation in the 1940's when products were often stable for only a few months and then only when refrigerated.

Table 31 is illustrative. It shows the expiration date originally established for certain items (as published in the Federal Register) and the increasingly long periods of product stability authorized by the Food and Drug Administration and published in subsequent issues of the Federal Register. The table lists only a few products as examples.

TABLE 31.—*Increased product stability for selected items as reflected in expiration date changes authorized by Food and Drug Administration*

Product	Expiration date (months)	Federal Register
Buffered penicillin powder	12	Dec. 30, 1948
	18	Aug. 3, 1950
	24	June 28, 1952
	36	Nov. 18, 1953
Penicillin ointment	[1] 6	Sept. 1, 1945
	[1] 12	Nov. 29, 1947
	12	Feb. 2, 1950
	18	Dec. 16, 1950
	24	Jan. 5, 1952
	[1] 36	July 25, 1953
Penicillin with streptomycin aqueous injection (dry form)	12	Aug. 23, 1950
	24	May 20, 1952
	36	Apr. 15, 1953
	48	Dec. 11, 1953
	60	Feb. 20, 1957
Chlortetracycline calcium sirup (oral)	12	Oct. 25, 1952
	18	Apr. 17, 1956
	24	Mar. 22, 1957
Chlortetracycline capsules	12	Aug. 13, 1949
	24	Oct. 5, 1951
	36	Apr. 12, 1952
	48	Sept. 10, 1953
	60	Oct. 6, 1955
Tetracycline hydrochloride oral suspension	12	July 13, 1954
	24	Jan. 27, 1956
Chloramphenicol capsules	12	Aug. 13, 1949
	48	Aug. 20, 1953
	60	June 18, 1954
Chloramphenicol palmitate oral suspension	12	Aug. 14, 1951
	18	Sept. 5, 1952
	24	Aug. 20, 1953
	36	June 18, 1954
	48	Apr. 12, 1955

[1] When under refrigeration.

CHAPTER V

Marketing Program of Antibiotics Manufacturers

Antibiotic drugs are promoted and sold in the same manner, and through the same channels of distribution, as are other pharmaceutical products. The word "promotion," as used in this chapter, signifies the efforts of drug manufacturers to sell their products.

Methods used in promotional activities are largely determined by the type of product to be distributed. In the field of pharmaceuticals, there are two general groups of products: (1) Those designated as "ethical" drugs, and (2) those classified as "proprietary" drugs.

"Ethical" drugs may be purchased from the druggist only upon presentation of a physician's prescription, or are dispensed only upon the recommendation of a physician.[1] Such "ethical" products are advertised primarily to physicians and to the drug trade.

"Proprietary" drugs are those which may be purchased from the druggist without a physician's prescription. These products are advertised to the general public, as well as to the drug trade.[2]

Antibiotics, generally, may be classified as ethical products. True, some antibiotics, particularly in the form of ointments, salves, and lozenges, are sold over the counter without a prescription because the antibiotic content of these preparations is so small as to preclude any untoward reaction on the part of the user. These over-the-counter sales are not considered in this chapter, since the total value of sales of such proprietary antibiotic products, according to the 1954 Census of Manufacturers, was less than 1 percent of all antibiotic products sold.[3]

A significant increase in the sale of ethical drugs occurred between 1947 and 1954. In 1947, about 61 percent of the dollar value of shipments of pharmaceutical preparations was in the ethical category, while in 1954 ethical preparations amounted to 72 percent of the total dollar value of shipments.[4]

The increasing use of such new products as sulfonamides, antibiotics, tranquilizers, and hormones is one of the principal reasons

[1] John G. Glover and William B. Cornell, "The Pharmaceutical Industry," The Development of American Industries, Prentice-Hall, Inc., New York, 1951, p. 459.

[2] Ibid., p. 459.

[3] Department of Commerce, Bureau of the Census, Census of Manufactures, 1954, Bulletin MC–28C, Drugs and Medicines, p. 10.

[4] Ibid.

why the proportion of ethical drug sales to proprietary sales has been increasing in recent years.[5]

Two of the principal purposes of this chapter are: (1) to indicate the particular antibiotic products (including trademarked brands of the same product) which have been promoted since 1945, including the time periods during which such products have been promoted; and (2) to describe the methods used in promoting these products. In order to accomplish both of these objectives, a survey of advertising of antibiotics in the Journal of the American Medical Association from 1945 through 1957 is incorporated in the section on journal advertising. Two other principal means of promoting antibiotics, detailing and direct mail, are described and discussed, but without extended reference to their use in the promotion of specific antibiotics. Although it is realized that journal advertising accounts for a smaller percentage of budget allocations for promotion than either detailing or direct mail, it affords a readily accessible and objective source of information regarding the promotional effort which has been devoted to particular antibiotics.

Promotional and Selling Efforts Directed Toward Physicians and Druggists

Promotional and selling efforts of ethical drug manufacturers are directed toward the medical profession[6] and pharmacists. Successful appeal to the physician is the primary objective. The unusual feature of this situation is that the physician himself is not normally the purchaser and consumer of the product.[7] However, without the physician's prescription, ethical drugs cannot legally be made available to the ultimate purchaser.

"Eighty percent or more" of the advertising "effort" of Abbott Laboratories, one of the leading manufacturers of pharmaceuticals, "is directed to physicians." The remainder is devoted to advertising to pharmacists, hospitals, veterinarians, dentists, and a very little to nurses.[8]

Modern Medicine Publications, Inc., sponsored a study of the factors which influence the selection of pharmaceutical products.[9] For this

[5] Ibid.

[6] The term "medical profession," as used in this chapter, includes not only practicing physicians but also dentists, hospital and clinical personnel, and student groups training for these fields. Advertising and promotion of antibiotics to veterinarians is not discussed in this chapter.

[7] Theodore Caplow, "Market Attitudes: A Research Report From the Medical Field," Harvard Business Review, November–December 1952, p. 105.

[8] Charles S. Downs, "Direct Results From Direct Advertising," Drug & Cosmetic Industry, September 1954, p. 316.

[9] Theodore Caplow and John J. Raymond, "Factors Influencing the Selection of Pharmaceutical Products," Journal of Marketing, July 1954, pp. 18–23. Table on p. 22.

study 182 physicians in the Midwest were interviewed to obtain a detailed picture of how physicians make their decisions about advertised therapeutic products. It must be borne in mind that this survey covered only a small sample of physicians, in one section of the country, and that it covered all pharmaceuticals rather than just antibiotics. One of the principal areas of interest in this study was the importance of each of the various channels of communication in providing the physician with information about drugs.

The first conclusion drawn from the study was that "ethical pharmaceutical products are normally adopted in response to the combined stimulus of several forms of advertising or communication." In only about 20 percent of the cases where new drugs were adopted was a single medium sufficient to secure the adoption. Detail men proved to be the strongest single influence in introducing new drugs, having introduced twice as many as direct mail and six times as many as journal advertising.

The second conclusion reached regarding product adoption was that "the relative influence of each advertising medium in stimulating the continued use of a pharmaceutical product is entirely different from its relative influence in introducing the same products."

While detail men are the most important means of introducing a product, other media, particularly journal advertising, are important in maintaining the doctor's allegiance to the product.

A basic part of this study involved an evaluation of the reasons for adopting a new product in preference to what the physician had been using previously. The following table which lists the motivating factors for making the switch indicates that the emphasis is placed on "operational characteristics" rather than "brand, price, packaging, or popularity":

Classification	Number	Percent [1]
Superior therapeutic effect	213	56.5
Side effects (presence or absence)	57	15.1
Ease of administration	54	14.3
Price	9	2.4
Confidence in house	7	1.9
Confidence in detail man	3	0.8
Experimental purposes	8	2.1
Patient preference	10	2.7
Other motives	16	4.2
Total	377	100.0

[1] Percentages calculated by Federal Trade Commission.

An important practical consideration makes concurrent advertising to retail druggists and physicians a vital necessity for manufacturers of ethical drug products. The nature of this practical consideration has been stated as follows: [10]

[10] Paul Klempter, "How an 'Ethical' Agency Operates," Advertising Agency and Advertising & Selling, July 1952, pp. 81, 132.

Drug-trade advertising is more important to the success of an "ethical" product than is generally realized. Although it is the physician who activates the sale, it is the druggist who actually rings the cash register. If the product which a physician prescribes is not in stock at the local drug store and the druggist cannot get it quickly from his jobber, a most unfortunate series of sales-killing events can take place. The druggist, of course, is not at liberty to change the physician's prescription. But he is free to phone the prescribing physician, suggesting a change to a competing product. When this happens, more harm is done than simply the loss of a single sale. Neither the physician nor the pharmacist appreciates being placed in this position, and their future attitude toward the original product can be most uncooperative. Thus, adequate drug-trade distribution must parallel the promotional campaign to physicians, and advertising to druggists plays an essential part in achieving this distribution.

Mass media, such as general magazines, newspapers, and network radio and TV, are not suitable for attracting and preserving the attention of these two relatively small groups.

Expenditures for Promotion

Promotion and selling expenses in the pharmaceutical industry and specifically in antibiotics account for a significant portion of the sales dollar. The ratio of these expenses to net sales varies by product, by company, and by year. The amount of money spent for such items as salesmen's compensation, advertising, and other components of selling and promotion depends on several factors: whether a product is (*a*) an exclusive or semiexclusive medical specialty, (*b*) a new product requiring extensive personal contact with doctors, (*c*) an already established product, or (*d*) a combination of conditions (*a*) and (*b*) or (*a*) and (*c*).

In response to a request by the Federal Trade Commission,[11] eight companies submitted information on their selling and promotional expenses for antibiotics. In 1956, these companies accounted for approximately 67 percent of the total net sales of antibiotics for the group surveyed.

According to the representations made by these companies, their promotional expenditures for antibiotics in 1956 ranged between 9.6 and 30.7 percent of total sales. They were allocated as follows:

Item	Percent of selling and promotion	Percent of total net sales
Salesmen's compensation	43.7	9.0
Other selling expenses	27.2	5.6
Samples	11.1	2.3
Direct mail	7.8	1.6
Periodicals	10.2	2.1
Total	100.0	20.6

[11] FTC data request, 1957.

These data indicate that the largest single promotional expense item for antibiotics by the eight manufacturers in the year 1956 was the compensation of salesmen.

The average percentage, 20.6, is identical with the average of promotional expenditures for 23 pharmaceutical firms, as reported in Modern Medicine Topics in July 1957.[12] The range of the percentages of these 23 companies was between 5.0 percent and 42.0 percent of total sales.

In the promotion of antibiotics, as in the promotion of pharmaceuticals generally, a decision must first be made as to which products to promote at any particular time, and next how much money and effort to put into each of the several channels of promotion. A typical promotional allocation for an ethical drug may be as follows:[13]

Method	Percent of promotional budget	
	New product	Old product
Personal selling	50	-----------
Journal advertising	10	15
Direct mail	15	70
Sales promotion devices	10	10
Exhibits and conventions	10	-----------
Other	5	5

It has been said that for every hundred products introduced, only 8 will be among the high-profit makers and best prescriptions sellers, 7 to 10 will pay their own way, and the others will fail.[14] This situation emphasizes the significance of the timing and direction of the promotional effort. The decision as to how much money and effort is to be put into each of the several channels of promotion is of prime importance.

Today, a manufacturer who introduces a new product must compete with products already well established or with extensively promoted brands of the same product offered by other manufacturers. A greater effort is required to introduce a new, unknown drug than is necessary to remind the medical and pharmaceutical professions of the availability of the established product.

The above allocations suggest that when a new product is introduced, the manufacturer probably emphasizes personal contact with physicians and druggists through his detail men. The function of the detail man is to explain to the doctor and the pharmacist the therapeutic advantages and utility of the new drug. It is likely that

[12] Modern Medicine Topics, July 1957. This publication is a monthly report compiled by Modern Medicine Publications, Inc., Market Research Department.

[13] Thomas A. Staudt, "The Promotional Mix," Drug & Cosmetic Industry, May 1957, p. 604.

[14] Ibid.

physicians and pharmacists, through reports of clinical studies and other sources, will already have heard of the product and will welcome an opportunity to discuss it.

Some idea of the allocation of promotional expenditures among the various media when a new antibiotic product is introduced is afforded by a pharmaceutical marketing study sponsored by the American Medical Association in 1954–55.[15] Five manufacturers of ethical drugs cooperated in this study: Ciba Pharmaceutical Products, Inc., Eaton Laboratories, Geigy Pharmaceuticals, Lederle Laboratories Division of American Cyanamid Co., and The Upjohn Co. Although the study proper was restricted to one market area in the vicinity of Fond du Lac, Wis., data were reported as to the total national promotional expenditure during a selected initial period of approximately a year after each of four ethical drugs were introduced. Total national promotional expenses for the fifth drug, Furadantin, were not made available.

The one antibiotic drug included in the study was Achromycin, Cyanamid's brand of tetracycline. As reported in the Fond du Lac Study, the first-year promotional budget for Achromycin totaled about \$2,447,000. This amount was allocated among the various media as follows: [18]

Detailing	\$1, 026, 000
Direct mail	851, 000
Medical journal advertising	470, 000
Exhibits at medical meetings	100, 000

Included in the expenditures for detailing were outlays for literature and the cost of free samples of Achromycin which were distributed. According to the Fond du Lac Study, monthly expenses for detailing were \$85,500 during the initial 12 months of Achromycin promotion. The following opinions were reported by the marketing organization which conducted the Fond du Lac Study: [19]

> A well-posted advertising authority referring to the broad spectrum antibiotics states that these products "had probably the largest promotional budgets ever used in the industry." A detail man remarked that "Lederle [American Cyanamid] was interested in bombarding physicians with the Achromycin name and we did just that and got the name across. We swamped them with Achromycin."

The direct mail budget of \$851,000 permitted 105 mailings, an average of two per week, to the full list of M. D.'s in the nation. There were also 7 mailings to dentists and 2 mailings to druggists.[20]

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[15] "The Fond du Lac Study," a basic marketing study presented by the American Medical Association, conducted by Ben Gaffin & Associates. Results were made available in 1956. Hereafter in citing this source, reference will be made only to the Fond du Lac Study and the particular report of this study used as source.

[18] "The Achromycin Story," the Fond du Lac Study, Report No. 12, 1956, p. 2.

[19] Ibid.

[20] Ibid.

Medical journal advertising was allocated among publications as follows: 26 insertions in the Journal of the American Medical Association, and monthly insertions in Modern Medicine, Medical Economics, 116 county journals, all State journals, regional journals, and most specialty journals.[21] The amount expended on this medium of advertising during the first year of Achromycin promotion was $470,000, according to the Fond du Lac Study.

Sales Promotion Techniques

Journal Advertising

In order to illustrate the nature and extent of advertising of antibiotics in medical journals during the years 1945–57, a page-by-page study of advertising in one of the nation's leading medical journals was undertaken by the Federal Trade Commission. For this purpose, the Journal of the American Medical Association was selected because of its wide circulation among practicing physicians and because of its relative frequency of publication, as compared with other medical publications and journals.

The aim of this survey was twofold—(1) to determine the ratio between advertising of antibiotics and advertising of other ethical products in the Journal by those pharmaceutical houses which manufacture both groups of products; and (2) to determine the antibiotics advertised most heavily in the Journal during particular years.

The year 1950 marked a significant shift, with respect both to the type of product advertised in the Journal and the manufacturers advertising most heavily. For this reason antibiotics advertising in the Journal will be discussed with reference to two time periods: (1) 1945–49; and (2) 1950–57.

The period 1945–49.—Table 32, below, presents a tabulation of advertising pages purchased in the Journal between 1945 and 1949 by 15 manufacturers of antibiotics. Most of these companies manufactured many other prescription drug products in addition to antibiotics during these years.

Four antibiotics were advertised in the Journal during 1945–49, inclusive: penicillin, streptomycin, dihydrostreptomycin, and tyrothricin. These were the principal antibiotics marketed during most of these years, although by 1949 two broad spectrums, Aureomycin and Chloromycetin, were reaching the market. Penicillin was by far the most heavily advertised of the four products during each of these years, attaining its maximum in 1947 when 98 pages of advertising of penicillin products appeared. Only 46 pages were devoted to the advertising of penicillin in 1948, and a mere 23 pages appeared in 1949.

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[21] Ibid.

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TABLE 32.—*Advertising by antibiotics manufacturers in the Journal of the American Medical Association: 1945–49*

[Number of pages]

Company	1945					1946					1947					1948					1949				
	P	T	S	O	I	P	T	S	O	I	P	T	S	O	I	P	T	S	O	I	P	T	S	O	I
Abbott	13			8	10	5			23	15	7			22	12	6			31	11	10			27	5
Bristol (Bristol-Myers)	2					12				1	16				20	8			1	14	2				2
Commercial Solvents	23				1	26					30				3	7					6				
Heyden	1										9					3									
Hoffmann-LaRoche	2			7	4				15	1				13	2										
Lederle (American Cyanamid)	1			8	17	4			25	6				22	1				5		1			20	3
Lilly	2				71				1	78	1			2	74	3			14	58	1			4	70
Merck	5			9	9	1		5	16	3	6		6	11	5	6		5	8	1	3		9	12	4
Parke, Davis	3			19	9		3		32	2		9		40	12				40	6				26	
Pfizer	6																	1							
Schenley	9				1	9				1	10				1										2
Sharp & Dohme		6		26	19		3		35	23		11					8		37					23	
Squibb	7			30	9	11			37	4	19			22	7	13		9	18	10				9	18
Upjohn	6			15	2				2	18				6	19				8	11				4	18
Wyeth (American Home Products)	3			27	17	1			31	10				43	6				60	1				70	4
Total	83	6		149	169	69	6	5	217	162	98	20	6	181	162	46	8	15	222	112	23		9	195	126

Abbreviations: P—Penicillin; T—Tyrothricin; S—Streptomycin; O—Other (nonantibiotic) products; I—Institutional.

Two observations may be made with respect to advertising of antibiotics in the Journal between 1945–49: (1) Little emphasis was placed upon trademarks in this advertising; rather, the generic names penicillin, streptomycin, or tyrothricin, or "a complete line of penicillin [or streptomycin or tyrothricin] products" were emphasized by the advertiser. As will be seen, this type of advertising diminished after 1950, with the appearance of patented antibiotics marketed by only one company or by a few companies. (2) There was a steady decline in the amount of antibiotics advertising after 1947, both in terms of the total number of pages of such advertising and as a percentage of total advertising in the Journal by the particular pharmaceutical companies listed in table 32.

The period 1950–57.—A comparison of advertising in the Journal of the American Medical Association by the companies surveyed in 1950 and in 1957 reveals the extent to which the increasing importance of antibiotic products was reflected in advertising in the Journal. There were 61 pages of antibiotics advertising in 1950. Advertising of other pharmaceutical products by the companies surveyed occupied 336 pages of the Journal. Institutional advertising filled 50 pages. The total number of pages of advertising in the Journal purchased by all companies surveyed in 1950 was 447.

TABLE 33.—*Advertising by antibiotics manufacturers in the Journal of the American Medical Association: 1950*

[Number of pages]

Manufacturer	Penicillin	Streptomycin	Broad spectrum	Other products *	Institutional	Total
Abbott				49	1	50
Lederle				45		45
Lilly	2			47	29	78
Merck	4	6		15	3	28
Parke, Davis			14	18		32
Pfizer			34		12	46
Sharp & Dohme				23		23
Squibb				54		54
Upjohn	1			22	5	28
Wyeth				63		63
Total	7	6	48	336	50	447

*Non-antibiotic.

TABLE 34.—*Advertising by antibiotics manufacturers in the Journal of the American Medical Association: 1951*

[Number of pages]

Manufacturer	Penicillin	Streptomycin	Bacitracin	Broad spectrum	Other products	Institutional	Total
Abbott	10				57		67
Commercial Solvents			2		1		3
Lederle				26	50		76
Lilly	2				47	25	74
Merck		7			26		33
Parke, Davis				11	15		26
Pfizer				99		1	100
Sharp & Dohme					10	18	28
Squibb					39	4	43
Upjohn					37	1	38
Wyeth					67		67
Total	12	7	2	136	349	49	555

TABLE 35.—*Advertising by antibiotics manufacturers in the Journal of the American Medical Association: 1952*

[Number of pages]

Manufacturer	Penicillin	Streptomycin	Broad spectrum	Other products	Institutional	Total
Abbott	4			60	1	65
Lederle				47		72
Lilly	2	4	25	44	24	74
Merck	4	4		67		75
Parke, Davis			21	26		47
Pfizer			70		[1] 228	298
Sharp & Dohme				22	2	24
Squibb	12			15	15	42
Upjohn	4			50		54
Wyeth				45		45
Total	26	8	116	376	270	796

[1] On June 21, 1952, Pfizer began publishing its house magazine Spectrum as a 12- to 16-page insert in the Journal on a semimonthly basis.

TABLE 36.—*Advertising by antibiotics manufacturers in the Journal of the American Medical Association: 1953*

[Number of pages]

Manufacturer	Penicillin specialties	Streptomycin	Broad spectrum	Other antibiotic specialties	Other products	Institutional	Total
Abbott	1	1		75	74		151
Commercial Solvents					1		1
Lederle			24		28	22	74
Lilly				32	26		58
Merck	[1] 1	2			51	4	58
Parke, Davis			5		20	4	29
Pfizer						[2] 579	579
Sharp & Dohme					10		10
Squibb					13		13
Upjohn	6				64		70
Wyeth	5				37		42
Total	13	3	29	107	324	609	1,085

[1] Not a specialty penicillin.
[2] 48 editions of Spectrum totaling 579 pages. Antibiotics advertised: Terramycin, Permapen, polymyxin bacitracin, streptomycin, dihydrostreptomycin, and Magnamycin.

TABLE 37.—*Advertising by antibiotics manufacturers in the Journal of the American Medical Association: 1954*

[Number of pages]

Manufacturer	Penicillin specialties	Boad spectrum	Other antibiotic specialties	Other products	Institutional	Total
Abbott			105	74	10	189
Lederle		97		54		151
Lilly			56	29		85
Merck				81		81
Parke, Davis		14		16	2	32
Pfizer					[1] 540	540
Squibb			8	5		13
Upjohn	3			119	2	124
Wyeth	9			45	1	55
Total	12	111	169	423	555	1,270

[1] 45 editions of Spectrum totaling 540 pages.

TABLE 38.—*Advertising by antibiotics manufacturers in the Journal of the American Medical Association: 1955*

[Number of pages]

Manufacturer	Penicillin specialties	Broad spectrum	Other antibiotic specialties	Other products	Institutional	Total
Abbott			46	93	13	152
Lederle		117		64		181
Lilly	9		29	22		60
Merck				48	18	66
Parke, Davis		58		3	14	75
Pfizer					[1] 528	528
Squibb	11		3	17	3	34
Upjohn		98		80		178
Wyeth	12			76		88
Total	32	273	78	403	576	1,362

[1] 44 editions of Spectrum totaling 528 pages.

TABLE 39.—*Advertising by antibiotics manufacturers in the Journal of the American Medical Association: 1956*

[Number of pages]

Manufacturer	Penicillin specialties	Broad spectrum	Other antibiotic specialties	Other products	Institutional	Total
Abbott	5		52	81	9	147
Lederle		138		84	8	230
Lilly	9		13	30		52
Merck			35	132		167
Parke, Davis		76		24	*22	122
Pfizer		32		63	211	306
Squibb	16	40	3	32	1	92
Upjohn			29	48		77
Wyeth	29			152		181
Total	59	286	132	646	251	1,374

*Pfizer discontinued insertion of Spectrum in the Journal during 1956.

TABLE 40.—*Advertising by antibiotics manufacturers in the Journal of the American Medical Association: 1957*

[Number of pages]

Manufacturer	Penicillin specialties	Broad spectrum	Other antibiotic specialties	Other products	Institutional	Total
Abbott	23		36	102	7	168
Bristol		90		13		103
Lederle		94		110	20	224
Lilly	28		21	56	2	107
Merck			9	82		91
Parke, Davis		68		75	21	164
Pfizer		4	8	46	10	68
Squibb	7	86	3	47	5	148
Upjohn		16		60		76
Wyeth	41			146	37	224
Total	99	358	77	737	102	1,373

By 1957, the number of pages of advertising of antibiotics had increased to 534. On the other hand, advertising of other pharmaceutical products occupied 737 pages, and institutional advertising 102 pages. Thus, there was a more than sevenfold increase in the advertising of antibiotic products in the Journal by the companies surveyed between 1950 and 1957. Advertising of nonantibiotic pharmaceutical products in 1957 was little more than twice the 1950 amount. A comparable increase occurred in institutional advertising.

It was after 1950 that the broad spectrum antibiotics attained their great market significance. Erythromycin and novobiocin were first marketed during the period 1950 to 1957. The advertising of these two products and of broad spectrum antibiotics under their various trademarks and trade names accounted for most of the increase in total number of pages of antibiotics advertising purchased by the companies surveyed.

The increase in advertising of penicillin products during these years is also noteworthy. In 1950, 7 pages were purchased for advertising penicillin. In 1957, 99 pages of advertising of penicillin products appeared. The trademarked specialties of particular companies were emphasized in all of the 1957 advertising of penicillin; for example, Abbott used 23 pages in the Journal to advertise Compocillin V and Lilly advertised two trademarked penicillin products: V-Cillin and V-Cillin K. These two products occupied 13 pages and 15 pages, respectively, in the Journal in 1957. Wyeth's advertising of antibiotics was limited to its penicillin specialty products, namely, Bicillin and Pen-Vee, which filled 22 pages and 19 pages, respectively.

Reports of clinical studies

Clinical studies are another important original source of information to the medical profession about new products. Articles reporting the results of these studies can be and frequently are directly related to promotion of ethical drugs. These articles actually are scientific accounts of some particular characteristics or effects of a new drug product when administered to patients suffering from particular maladies. Studies of this sort may be done by scientists in the employ of the manufacturer of the product, or they may be undertaken by independent physicians or by specialized clinics at the request of a manufacturer.

Direct mail advertising

Direct mail advertising is one of the principal means of drug promotion. It is a very flexible technique, in the sense that the subject matter or the frequency of mailings can be quickly changed. There

are, furthermore, many different types of printed matter which may be used for direct mail advertising and promotion; for example, house magazines, newsletters, manuals, prescription blanks, and illustrated brochures and leaflets.

Most of the leading pharmaceutical manufacturers which produce antibiotics publish regular house magazines, printed on high-quality paper and with a very attractive format. Examples of these publications are Abbott's "What's New," Upjohn's "Scope Weekly," "Squibb Memoranda," Sharp & Dohme's "Seminar," Lilly's "Physicians Bulletin," Parke, Davis' "Therapeutic Notes," and Pfizer's "Spectrum." In an October 1952 article entitled "How To Play the House Organ," Fortune Magazine comments: "There are house organs such as Scope, which the Upjohn Co. publishes for doctors, that are more elegant than any newsstand magazine." [22]

A second category of printed matter mailed to physicians or druggists may be classified as "service material." The following are examples of service material.[23]

(1) Manuals relating to specific subjects;
(2) Anatomical drawings or photographs;
(3) Handbooks;
(4) Reference books;
(5) Descriptive catalogs;
(6) Medical journal abstracts;
(7) Printed prescription blanks.

The third general category of direct mail advertisements encompasses brochures and other matter designed for quick reading by the physician. They are usually elaborately illustrated, with the name of a particular product and indications for its use.

Exhibits at conventions

Still another area in which printed advertising matter is useful in the promotional effort is in supplementing or complementing exhibits at medical meetings. For most advertising budgets, this type of promotion represents a smaller proportion of the total allocation than other forms of promotion such as detailing, direct mail, and journal advertising. The first-year promotional budget for Achromycin, with $100,000 allocated for medical exhibits, out of a total of $2,447,000, has been previously discussed.

The detailing system

Undoubtedly the most important method used in promoting the sale of ethical drugs is detailing. It accounts for the largest share of

[22] Fortune, October 1952, p. 144.

[23] Robert A. Hardt, "Product Development, Promotion, and Marketing," Drug Research & Development, New York; Revere Publishing Co., 1948, p. 469.

the promotional dollar and appears to be the most effective means of selling. The detail man represents some particular pharmaceutical manufacturer. His job is to call upon physicians personally, introduce and promote new products to them, and answer questions relating to his company's products. He also serves as a channel of communication from the physician to the manufacturer. The principal function of the detail man has been described as follows: [25]

> The task of the detail man, however, is not merely educational or abstractly professional. Indeed, the major objective of detailing is the development of the doctor's interest to the point where he will actually prescribe the product before him. For no matter how informed the detail man is or how well he explains the nature and purpose of the drug, no interview with the doctor can be termed successful unless it induces a prescription or sale. Of course, the prescription need not be written immediately, but, generally speaking, use of the product should follow the detail man's call, or the interview may be considered a failure. This aspect should be emphasized in training. The detail man should be impressed with the fact that the primary, if not sole, purpose of his call is to develop prescriptions or recommendations for his company's products.

A typical detail man for one of the major pharmaceutical manufacturers may have a territory which includes 200 doctors, 40 retail drugstores, and 10 hospitals. Some of the manufacturers have detail men who are assigned exclusively to hospitals.

Available data indicate how extensive the detailing was when Achromycin, American Cyanamid's brand of tetracycline, was first introduced in late 1953. The Cyanamid detail man in the area of Fond due Lac, Wis., had about 300 doctors in his territory and managed to see 150 or 160 of them every month, devoting the most attention to heavy prescribers.[26] Some doctors were visited three times a month, some once a month, and others only occasionally. The largest volume druggist in the area was visited once a week, the least busy druggist once a year, with calls upon other druggists and pharmacists varying between these extremes. During his first visit the Cyanamid detail man checked to make sure that all pharmacists had received supplies of the 250-milligram capsule form of Achromycin.

As other Achromycin products were added to the line later on, the detail man employed different detailing techniques with different doctors.[27] Capsules and tablets would be shown to one doctor, and samples of the product left with him. As new dosage forms were introduced, the detail man would concentrate on one or the other of them; for example, the cherry-flavored oral suspension. Where doctors appeared to be disinterested in one dosage form, other dosage

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[25] Thomas H. Jones, " 'Detailing' the Physician," Drug Research & Development: Revere Publishing Co., New York, 1948, p. 520.

[26] "Effectiveness of Promotion in a Medical Marketing Area," a special report prepared for the American Medical Association by Ben Gaffin & Associates in 1956.

[27] Ibid.

forms were shown to them. Most of the physicians were already aware of Achromycin before the detail man's visit, as a result of journal articles, journal advertising, and direct mail.

Eight of the leading antibiotics manufacturers spent approximately $70 million for salesmen's and detail men's compensation and expenses. These 8 companies employed about 5,600 detail men.[28] Taking into consideration the salaries of salesmen other than detail men (selling principally industrial chemicals and proprietary pharmaceuticals), travel allowances, and miscellaneous expenses, it seems likely that the average detail man receives about $7,000 per year in compensation. Most of the antibiotics manufacturers indicate that the detail men they employ receive a fixed salary, plus a bonus or commission.

Estimates of the total number of detail men employed by pharmaceutical manufacturers range from 10,000 to 12,000 of which about 7,000 were employed by 10 of the companies which manufactured antibiotics in 1956. One manufacturer of antibiotics, Commercial Solvents Corp. does not employ detail men. Among the pharmaceutical manufacturers which make antibiotics, there has been a substantial expansion in the sales forces in the last decade. This increase coincided with the introduction of antibiotics, hormones, tranquilizers, and many other new ethical pharmaceutical products.

It has been estimated that the cost of calling on a physician is probably between $6.50 and $7.50 per call.[29] If the lower cost per call is used, the annual cost of calling on each of the approximately 150,000 practicing physicians in this country 6 times a year would be about $6 million.

It would appear that expenditures of this magnitude can generally be undertaken only by the large pharmaceutical manufacturers. Smaller firms are, therefore, forced to compromise either by calling on fewer physicians or by spacing their calls at longer intervals.

Distribution of free samples

The vice president of Abbott Laboratories has stated "* * * there is a sort of sales magic in samples."[30] He describes the advertising importance of drug samples in the following language:[31]

> Place a sample in the hands of the physician, or, in appropriate cases, the dentist, nurse, or veterinarian. Let the prospect see, handle, taste, smell, or feel the product. The sample may be small, far too small in many instances to observe its effect upon even one patient. Despite this, the sample in many instances will do more than any other type of advertisement to register the name

[28] FTC data request, 1957.

[29] John D. McEvilla, "Competition in the American Pharmaceutical Industry," Ph. D. thesis, University of Pittsburgh, 1957, p. 123.

[30] Charles S. Downs, "Advertising," Drug Research & Development, Revere Publishing Co., New York, 1948, p. 485.

[31] Ibid.

of the product and its uses in the prospect's mind. Practically the only ethical drug products whose sales will not be benefited greatly by sampling are the rare medicaments distinguished by advantages so great that in simple justice to the patient their actual use is called for.

When American Cyanamid introduced Aureomycin in 1948, 10 carloads of samples were mailed to about 142,000 physicians. It has been estimated that the cost of the product alone was about 2 million dollars.[32]

Miscellaneous promotional techniques

Several methods of promotion cannot be classified under any of the headings previously discussed. These methods are important, however, and deserving of mention. Among these methods are the following:

(1) Sponsorship of regional or local medical meetings in cooperation with regional or local medical societies.
(2) Motion pictures.
(3) Closed-circuit television programs.
(4) Guided tours and lectures.
(5) Novelties.

The Introduction of Terramycin

An outstanding example of successful promotion in ethical drugs was the introduction of Terramycin. Prior to 1950, Chas. Pfizer & Co., Inc., did not sell drug products under its own label to the retail drug trade. By 1957, Pfizer had become one of the leading sellers in the market for packaged trademarked antibiotic products. The success of Pfizer's promotion of Terramycin, described by Business Week as "The Terramycin Blitz" [33] played no small part in Pfizer's entry into the sale of antibiotics to the wholesale and retail drug trade. This campaign will be described in some detail in order to show how the promotional techniques heretofore discussed may be effectively utilized in attaining the advertiser's objectives. When Pfizer's research staff discovered and developed what appeared to be a highly promising new antibiotic, Terramycin, which no competitors would be able to market once Pfizer could obtain a product patent,[34] a decision had to be made as to how this product should be distributed.

On February 9, 1950,[35] the Pfizer board of directors voted to change its traditional marketing policy, and commence selling directly to

[32] John D. McEvilla, "Competition in the American Pharmaceutical Industry," Ph. D. thesis, University of Pittsburgh, 1957, p. 143.
[33] Business Week, October 13, 1951.
[34] Pfizer did obtain a patent on this product in the summer of 1950. See pp. 232 for a more detailed discussion of the issuance of this patent.
[35] Sales Management, March 1, 1951, p. 76.

retailers, wholesalers, and hospitals, notwithstanding the fact that Pfizer had had no experience in selling directly to these groups and had no sales force adaquate to undertake the promotion of ethical drug products. The unfavorable aspect of this situation was that two formidable competitive products, Chloromycetin and Aureomycin, were already established in the market and were being intensively promoted by "two major competitors [Parke, Davis and Lederle] with a combined 1,300-man sales force and 137 years of retail trade distribution experience." [36]

On March 15, 1950, the Pfizer sales organization was composed of a sales manager, an advertising manager, and eight detail men. A further complicating factor from Pfizer's point of view was that although the end of March had been established as the deadline for introducing Terramycin to the market, Pfizer's application submitting the product to the Food and Drug Administration had not yet been acted upon—and according to Federal law, a new drug may not legally be introduced into interstate commerce until the Food and Drug Administration has determined that the new drug is safe. Still another obstacle to promotion of the drug was the long-established policy of the Journal of the American Medical Association against advertising a product name before approval of the drug by by the American Medical Association. This approval had not yet been given for Terramycin.

Confronted with the realities of the situation, Pfizer first retained the William Douglas McAdams advertising agency, which specializes in the promotion of ethical drugs.[37] Next, it was decided that the sales force could be most effectively utilized by concentrating its initial effort on one key point in the distribution system. In 1948, the market for ethical drugs was composed of the following groups:

Wholesalers	About 800.
Retail drug outlets	About 41,000.
Hospitals	About 7,000.
Physicians	About 150,000.

It was decided to concentrate efforts of Pfizer's sales force on the wholesaler and then shift to hospitals. On March 15, telegrams were sent to individual wholesalers throughout the nation, alerting them that Pfizer would be able to release Terramycin for sale as soon as clearance came from the Food and Drug Administration.[39] A special telephone switchboard was installed by Pfizer in anticipation of approval of the product. Immediately upon receiving clearance, on March 22, Pfizer's eight-man detail staff commenced selling Terramy-

[36] Modern Packaging, May 1952, pp. 138–142.
[37] Business Week, October 13, 1951, p. 134.
[39] Ibid., p. 136.

cin by telephone to leading wholesalers throughout the country. An added inducement to wholesalers, according to Business Week, was the offer of a "better than average discount."[40] Within an hour after Food and Drug Administration's release of Terramycin, the drug was being shipped to many wholesalers. Following completion of the detailing-by-telephone, Pfizer's eight-man sales force, each man equipped with elaborate visual aids, set out to contact all wholesalers personally. Traveling by air, working at night and weekends, the detailing force was able to complete the scheduled wholesale circuit in 2 weeks.[41] Meanwhile, an extensive direct mail campaign featuring Terramycin was undertaken. For a period of 3 months, mailings to retail druggists, wholesalers, physicians, and hospitals averaged over 1 a week, with as many as 2 or 3 mailings in some weeks.

Not until July 27, 1950, did the American Medical Association give its approval to Terramycin. Until that date it was therefore impossible to advertise Terramycin in the Journal of the American Medical Association. Commencing with the April 15, 1950, issue of the Journal, however, Pfizer ran a series of institutional advertisements with "Terra" as the theme, for example, "Terra firma," "Terra bona," "Terra fertilis," etc. This continued until July, when Pfizer was allowed to advertise its product "Terramycin."

The detailing of physicians remained a problem. By mid-April, the detailing force was composed of only 20 men, still far too small to permit effective detailing of individual physicians. To remedy the situation, a hospital promotion project was inaugurated. Displays presenting information about Terramycin were set up in hospital staff rooms, each display attended by a Pfizer detail man. This procedure permitted the group detailing of many doctors in a comparatively short time. Pfizer estimated that 30,000 physicians were contacted in this manner within a period of time during which only 5,000 physicians could have been contacted had the customary method of individual detailing been followed.[42]

By September of 1951, Pfizer had upped its sales force to include about 300 detail men.[43] The success of Pfizer's promotional effort may be gauged from the fact that by 1951 Terramycin had captured about 24.4 percent of the total medicinal broad spectrum market. This compared with Aureomycin's 48.5 percent and Chloromycetin's 27.1 percent of the market. Both of these last-named products were introduced more than 1 year prior to Terramycin. Nevertheless, as mentioned above, both Lederle and Parke, Davis had much larger sales forces, and a long history of ethical drug promotion.

[40] Ibid.
[41] Sales Management, March 1, 1951, p. 78.
[42] Ibid.
[43] Business Week, October 31, 1951, p. 131.

Channels of Distribution

In general, the marketing channels for ethical drugs and for proprietary drugs are similar. Both types move through wholesalers, retail drugstores, and hospital pharmacies. The principal difference is that ethical drugs, except for the minor amount sold over the counter, are either dispensed by a physician or can be purchased only with a doctor's prescription.

Due to the scarcity of information concerning the distribution of antibiotics as a distinct group, this part of the chapter deals with the marketing of ethical drug products as a whole.

Wholesaler

The drug wholesaler plays an important part in the distribution of ethical preparations. The number of general-line drug wholesalers increased from 297 in 1939 to 304 in 1948, and to 392 in 1954. There were also 461 specialty-line drug wholesalers selling pharmaceuticals in 1954.[45] Sales of both groups in 1954 totaled about $1,400 million, an increase of some $417 million over 1948.[46] This figure includes sales of pharmaceuticals and biologicals, proprietary medicines, druggists' rubber goods, cosmetics, toiletries, and related merchandise.

The total sales by drugstores in 1954 were about $5.3 billion, and the cost to the druggists of these goods was about $3.6 billion.[47] This means that approximately one-third of the purchases of retailers were through wholesalers (since wholesalers' sales were $1.3 billion and about 95 percent of these sales went to retailers). When the practice of direct purchasing by chain drugstores is taken into consideration, it would appear that approximately 50 percent of the purchases of individually owned drugstores were made through wholesalers.[48]

It has been estimated that about 35 percent of the total sales of wholesale druggists are in drugs, chemicals, and pharmaceuticals.[49]

The wholesale drug operation of McKesson & Robbins accounts for about one-third of the sales of all wholesale drug houses. The total sales of McKesson & Robbins in 1956 were about $530 million, of which 65 percent, or about $345 million, was in wholesale drugs.[50] There are several large local chains of wholesalers, among the largest being Southwestern Drug Corp. of Dallas; Fox-Vleit of Wichita, Kans.; and Brunswig Drug of Los Angeles.

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[45] Department of Commerce, Bureau of the Census, Census of Business, 1954, Wholesale Trade, Series PW 3–45.

[46] Ibid.

[47] Paul C. Olsen, Marketing Drug Products, Rutgers University Press, New Brunswick, 1955, p. 209.

[48] Ibid.

[49] Ibid., p. 211.

[50] Moody's Industrial Manual, 1957, p. 38

A study made by the Policy Committee of the Drug Industry disclosed that the wholesaler was the main supply source for prescription chemicals. In the group of retail stores studied, the percentage of total purchases made from wholesalers ranged from 35.7 to 92.1 percent, with the average at 64.7 percent.[51]

Retail drugstores

According to an estimate made by Modern Medicine Publications, Inc., in 1953, about 25 percent of retail drugstore prescription sales were in antibiotics. Approximately 20 to 25 percent of the sales of all retail drugstores are in the prescription category, which means that about 5 percent of the average drugstore's sales are in antibiotics. About 90 percent of all prescriptions are dispensed through drugstores, and the remainder are dispensed by physicians, hospitals, and clinics.[52]

The significance of changes taking place in medicinals is indicated by this excerpt from Drug Store Operating Costs and Profits:

> Perhaps no other drugstore department has experienced the revolution that has taken place in the prescription department in the last several years. The introduction of countless new pharmaceutical specialties, particularly the sulfa drugs, antibiotics, antihistamines, and hormones, has changed the character of the druggist's prescription business from a compounding to a dispensing operation. Well over 80 percent of all prescription sales today are dispensed prescriptions.[53]

The 1954 Census of Business reports a total of 44,511 retail drugstores with payroll, doing a total sales volume of about $5 billion. This represents an increase of about 3,000 outlets and $1.5 billion in sales over 1948. The classification "drugstores with payroll" does not include the small stores which are operated as a family venture.

The retail drugstores generally handle a full line of antibiotics. As mentioned previously, some of the antibiotics are sold over the counter and do not require a prescription. For the most part, these are antibiotics such as bacitracin, neomycin, and gramacidin, which are sold in ointments and salves intended for local application for minor infections and irritations. Penicillin and streptomycin, which are usually administered parenterally (by injection), are sold to physicians by the drugstore in ampoules or vials. These purchases by physicians are made either directly from the retail druggist or by use of a "turnover order" placed with the druggist by the sales representative of the pharmaceutical manufacturer. The broad spectrum

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[51] Burley, Fisher, and Cox, Drug Store Operating Costs and Profits, McGraw Hill, New York, 1956, p. 238.

[52] Paul C. Olsen, Marketing Drug Products, Rutgers University Press, New Brunswick, 1955, p. 99.

[53] Burley, Fisher, and Cox, Drug Store Operating Costs and Profits, McGraw Hill, New York, 1956, p. 219.

antibiotics and some of the newer forms of penicillin are usually sold in tablet or capsule form for oral dosage.

A recent survey indicates that the retail druggist is becoming an increasingly important source of information for the doctor.[54] The ethical pharmaceutical manufacturer recognizes this trend, and most of them are devoting an increasing amount of time calling on the retail druggist and acquainting him with their new products. According in a recent survey, the average urban druggist receives visits from 18 doctors in the course of a year, and the average number of visits per doctor per year is 28. The rural druggist sees only 8 doctors, but each one visits him 60 times a year. This gives the druggist approximately 500 opportunities to assist physicians in obtaining information about pharmaceuticals.[55]

Hospitals

It has been estimated that approximately $250 million are spent annually for ethical pharmaceuticals in the 7,000 hospitals in this country. This comprises about 27 percent of all ethical pharmaceutical sales.[56] Approximately 30 percent of the hospital purchases of drugs and chemicals in a recent year were antibiotics.

The following is a breakdown of hospital purchases of antibiotics:[57]

	Dollars (thousands)	Percent
All antibiotics	67,725	30.10
Broad spectrum	30,285	13.46
Nontrademarked penicillin	8,685	3.86
Streptomycin and dihydrostreptomycin	2,160	.96
All other antibiotics	26,595	11.82
Total all drugs and chemicals	225,000	100.00

A little more than half of all hospitals, accounting for 86 percent of the total bed complement, have pharmacies.[58] Some smaller hospitals depend on nearby retail pharmacies for needed pharmaceuticals and related products, or have a pharmacy or drugroom but do not employ a registered pharmacist. In these cases, the dispensing is usually done by an intern or nurse. The number of prescriptions dispensed in the average hospital pharmacy is several times the national

[54] Journal of the American Pharmaceutical Association, Practical Pharmacy Edition, September 1952, p. 660.

[55] American Druggist, May 6, 1957, p. 6.

[56] Hospital Pharmacy, prepared by Journal of American Hospital Association, revised September 1954, p. 2.

[57] William E. Hassan, Jr., "Antibiotics in the Hospital Pharmacy," Journal of the American Pharmaceutical Association, Practical Pharmacy Edition, November 1954.

[58] Hospital Pharmacy, prepared by Journal of American Hospital Association, revised September 1954, p. 10.

average for all other pharmacies. About 17 percent of large hospitals (500 beds and over) manufacture their own solutions for injection.[59] A recent survey conducted by the research department of Modern Medicine Publications, Inc., indicates that the medical staffs of hospitals, either individually or as a group, carry a great deal of weight in the final decision as to which pharmaceuticals to stock.[60]

A survey conducted by Hospital Management magazine among some 40 smaller hospitals disclosed that there were actually 27 different bases in charging patients for medication.[61]

Some of the methods were:

(1) Cost doubled. Minimum charge on hypodermics, 50 cents.
(2) Cost plus 40 percent on most.
(3) Charges as per local retail drugstores.
(4) Cost doubled on most, more on some.
(5) Cost plus 60 percent.
(6) Drug charges made by local retail pharmacy. Hospital has no charge.

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[59] Ibid, p. 12.
[60] Modern Medicine, Medical Market Guide, 1956, p. 28.
[61] Daniel F. Moravec, "Pharmacy Service in Smaller Hospitals," Hospital Management (reprint, no date).

Chapter VI

Pricing in the Antibiotics Industry

In this chapter the price histories and pricing behavior of the major antibiotics—the principal penicillins, the streptomycins, and the so-called broad spectrums—are considered for the period covered in this report. These are the most widely used antibiotic products. Following the introduction of sodium, potassium and procaine penicillin, streptomycin, and dihydrostreptomycin, prices of these products declined steadily until the end of 1955. In 1956, the prices to some classes of customers increased. Prices of the first three broad spectrums declined from the time of their introduction into the market—Aureomycin, in 1948, Chloromycetin in 1949, and Terramycin, in 1950—until October 1, 1951, but remained unchanged to the drug trade thereafter. The fourth broad spectrum antibiotic, tetracycline, was introduced in 1953 and has remained at the price level which has prevailed for broad spectrum antibiotics since October 1, 1951. Prices of certain penicillin specialties, for example, benzathine penicillin and phenoxymethyl penicillin (penicillin V), which were introduced after October 1, 1951, at the approximate price level of the broad spectrum antibiotics, have not changed since their introduction.

This chapter describes the price histories of these antibiotics and seeks to relate the economic factors underlying their production and distribution to their price structure. Other antibiotics, including erythromycin and novobiocin, each of which has been made by more than one manufacturer, and a number of single-company specialties, as well as the various combinations of antibiotics, are not considered in detail in this chapter.

The channels through which medicinal antibiotics are distributed are the same as those through which older drugs and medical supplies move. Moreover, most antibiotics are sold only on prescription and it is the physician who, on the basis of his judgment as to the effectiveness of different antibiotics, decides which antibiotic he will prescribe. Beyond this, however, antibiotics production and distribution present a number of noteworthy characteristics. Among these are (1) the newness of the industry, (2) the rapidity of its growth based on clinically demonstrated effectiveness of its products, (3) the similarity in the production techniques used in the biosynthetic preparation of most of them, and (4) the patent ownership and patent

licensing situation as it has affected the number of manufacturers engaged in production and distribution of such antibiotics as the common salts of penicillin, the streptomycins, the broad spectrums, and certain penicillin specialties. The economic factors relating to the pricing of antibiotics are discussed under the following subheadings of this chapter:

Factors Affecting the Supply of Antibiotics.
Factors Affecting the Demand for Antibiotics.
The Marketing System and Antibiotic Prices.
Price Histories of Selected Antibiotics:
Price History of Selected Penicillin Products.
Comparative Price Levels of Selected Antibiotics.
Price History of Selected Streptomycin Products.
Government Procurement of Penicillin and Streptomycin.
Price History of the Broad Spectrum Antibiotics.
Government Procurement of Broad Spectrum Antibiotics.
The Market Share of Each Broad Spectrum Relative to Total Broad Spectrum Sales, 1951–56.

Factors Affecting the Supply of Antibiotics

Penicillin

Prior to February 1, 1943, the trickle of extremely high cost penicillin which the producers were able to supply had been given free of charge for use in clinical testing. On February 1, 1943, when the price of penicillin was established by the Government at $200 per million units, the new antibiotic had successfully passed the hurdle of clinical acceptance which every new drug must surmount. In 1943, every clinical test had proved it to be superior to previously used drugs in a wide range of therapies. But it was still impossible to produce it in large quantities at low cost.

By the end of 1945, however, the commercial producers of penicillin had applied various technological and scientific discoveries with such success that mass production of penicillin became a reality.

As discussed in chapter IV of this report, the fundamental technique employed in the commercial production of antibiotics is the deep-vat fermentation process. Application of this process to the production of organic acids was discovered and patented by Dr. Orville May, Dr. Andrew Moyer, and other scientists employed by the Department of Agriculture. This basic advance in fermentation technology was later adapted to the production of antibiotics. Another important process patent covering the use of corn steep liquor as a nutrient medium for the production of penicillin was obtained later by Dr. Moyer. Both the deep-vat fermentation process and the corn-steep-liquor process contributed to an enormous increase in yields of

penicillin, and the patents on both of these processes were freely licensed to all domestic applicants.

An additional vital contribution to the increase in penicillin yields was the development of a more productive micro-organism. This was accomplished by scientists working in research laboratories at the Carnegie Institution and the University of Wisconsin, and was made available to all manufacturers.

The cost of production per unit of penicillin plummeted as these discoveries were applied and refined by the various manufacturers. Competition among them for shares in the market resulted in prices which declined steadily through the 1940's and early 1950's. By 1955, the published price of penicillin charged by the retailer had fallen to about 60 cents per million units, as compared with the original price of $200 per million units paid by the Government in 1943 for very small quantities of penicillin then available. (The $200 price had been established at a time when penicillin production was in a very primitive stage, of course.)

The knowledge gained in the application of these improved techniques to production of penicillin became an invaluable asset to the industry when streptomycin and the broad spectrum antibiotics were later discovered. This was because the same biosynthetic processes employed in the production of penicillin could be used in producing these new antibiotics.[1]

In addition to development and application of the freely available techniques mentioned above, there were few patent restrictions on the entry into the manufacture of penicillin during the years 1943–50. Penicillin itself was discovered by Alexander Fleming in England in 1928, and he never applied for a patent on this product in the United States. The product was therefore in the public domain.[2]

As distinguished from the common salts of penicillin, however, such as sodium penicillin, potassium penicillin and procaine penicillin, which have either not been patented, or the patents of which have been widely licensed, mention should be made of certain more recently developed and patented penicillin products. Among these are benzathine penicillin and phenoxymethyl penicillin, first marketed in 1951 and 1955, respectively. The manufacturers' prices of each of these patented products have remained uniform and unchanged since they were introduced.

Streptomycin

Scientists at Rutgers University, working under research grants by Merck, discovered streptomycin. A research foundation at Rutgers

[1] The only antibiotic which so far has been successfully chemically synthesized for commercial production is chloramphenicol.

[2] Prior to 1949, chemical compositions could not be patented in England.

University ultimately obtained a product patent on this invention and has followed a policy of licensing at a stipulated royalty rate all qualified companies wishing to undertake the manufacture and sale of streptomycin.

The next important antibiotic discovery was dihydrostreptomycin, a modified form of streptomycin. A patent on this product was issued to Merck & Co., which followed a policy of licensing at reasonable royalty rates any companies desiring to manufacture this product.

Thus, as a result of an already existing production technology developed in connection with penicillin, much of which could be applied to the production of streptomycin, and the liberal licensing by the research foundation at Rutgers University and by Merck & Co. of patents on streptomycin and dihydrostreptomycin, respectively, numerous manufacturers entered into the production and distribution of these antibiotics. The manufacturers made great strides in further perfecting their production techniques. All of these factors provided the means for adequate supply of streptomycin and dihydrostreptomycin to the public and resulted in a continuous and steady price decline at the manufacturer's level down to 1956. Three of the manufacturers ceased to produce streptomycin and dihydrostreptomycin in the course of the period covered by this report.

Since the discovery of penicillin, streptomycin, and dihydrostreptomycin, many new and important antibiotic substances have been discovered. The basic production techniques applied in connection with the manufacture of penicillin and streptomycin are also used in the commercial production of most of these later antibiotics. In fact, as already noted, chloramphenicol (Chloromycetin), produced by Parke, Davis & Co., is the only antibiotic product currently being manufactured exclusively through the use of techniques not involving fermentation of micro-organisms.

Broad spectrum antibiotics

There are certain characteristic features which must be considered with respect to the supply of the broad spectrum antibiotics.

The four antibiotics which now comprise the broad spectrum group are: chlortetracycline (Aureomycin), oxytetracycline (Terramycin), tetracycline, and chloramphenicol (Chloromycetin). These four antibiotics represented 24.3 percent by weight of all antibiotic products for medicinal purposes and accounted for approximately 50 percent of total medicinal dollar sales of antibiotics at the manufacturer's level in 1956. Although chloramphenicol is manufactured by a production technique completely different from that employed in the commercial production of the penicillins and the streptomycins, the three remaining broad spectrum antibiotics are produced commer-

cially by the use of a technology closely similar to that which is employed in the commercial production of penicillin, streptomycin, and dihydrostreptomycin. Further, the production facilities used for all except chloramphenicol are largely interchangeable. Thus, expansion of production facilities for any one antibiotic represents potential capacity for the production of others as well. Through the use of these closely similar production methods, the yields obtained from fermentation of the three tetracyclines, i. e., chlortetracycline, oxytetracycline, and tetracycline, have approximated, if not exceeded, those obtained in the fermentation of penicillin and the streptomycins.[3]

Limitations on the number of manufacturers of chlortetracycline, oxytetracycline, tetracycline, and chloramphenicol have resulted from patent ownership and the pattern of patent licensing which exists as regards these broad spectrum antibiotics. Three of these products, whose trade names are Aureomycin, Chloromycetin, and Terramycin, are manufactured and marketed exclusively by the respective patent owners, Cyanamid, Parke, Davis & Co., and Pfizer. Tetracycline, the most important broad spectrum, is the subject of a series of licensing and cross-licensing arrangements between Pfizer, the owner of the product patent, and Cyanamid, Bristol Laboratories, Inc., Olin Mathieson Chemical Corp. (E. R. Squibb & Sons), and The Upjohn Co. The latter two companies, Olin Mathieson and Upjohn, are licensed to sell tetracycline, but may not manufacture this antibiotic.

These five companies account for about 80 percent of the sales of all so-called broad spectrum antibiotics. The patenting and licensing of tetracycline are discussed in detail in chapter VIII. The only other broad spectrum, Chloromycetin, is manufactured and sold exclusively by the patent owner, Parke, Davis & Co. From the foregoing, it is apparent that the supply of each of the broad spectrum antibiotics is subject to much greater control than is possible with respect to the supply of the older common salts of penicillin and the streptomycins.

Following the introduction of Aureomycin in December 1948, broad spectrum prices declined when Chloromycetin and Terramycin were introduced in 1949 and 1950, respectively. The introduction of each new broad spectrum antibiotic was anticipated by price reductions of those broad spectrums already on the market. The last reduction in price for this group of products, to the date of writing, occurred on October 1, 1951. Thereafter, published prices of broad spectrum antibiotics remained unchanged insofar as retailers, hospitals, and consumers were concerned. The fourth broad spectrum, tetracycline,

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[3] Encyclopedia of Chemical Technology, the Interscience Encyclopedia, Inc., New York: Vol. 13, p. 779, table I. British Patent No. 781,843, p. 2, lines 115–121, owned by American Cyanamid Co. See also ch. IV, pp. 119–122, of this report.

was first marketed in 1953 at the price which had prevailed for the other three broad spectrums since October 1, 1951. This price structure remained in effect through 1956, the period covered by the present report.

Table 9, page 74, shows the extent to which medicinal market supplies of penicillin, streptomycin, dihydrostreptomycin, chlortetracycline (Aureomycin), oxytetracycline (Terramycin), chloramphenicol (Chloromycetin), and tetracycline increased between 1948 and 1956.

As the data in this table reveal, output of penicillin for medicinal purposes increased from 156,000 pounds in 1948 to 886,000 pounds in 1956, and output of streptomycin and dihydrostreptomycin for medicinal uses increased from 84,000 pounds in 1948 to 622,000 pounds in 1956.

In 1948, the production of broad spectrum antibiotics was negligible; penicillins, streptomycin and dihydrostreptomycin accounted for 99.7 percent by volume of total production of antibiotics for medicinal use. In 1956, production of these three older antibiotics was greatly increased, but their proportion of the total production of all antibiotic substances for medicinal uses had decreased to about 68 percent, due principally to rapid increase in the production of broad spectrums.

Among the latter, chlortetracycline (Aureomycin) was the original tetracycline product to be marketed, with only 661 pounds of this antibiotic reaching the market in 1948. Subsequently, in 1949, 1950, and 1953, respectively, chloramphenicol (Chloromycetin), oxytetracycline (Terramycin), and tetracycline were marketed. In 1956 over 535,000 pounds of the four broad spectrums were marketed, representing 24.3 percent by volume of all antibiotics produced for medicinal purposes.

Contributing to the increase in supply of antibiotics was the great expansion of production facilities in the antibiotics industry which took place during the Korean War years 1951–53. As shown by table 23, page 104, during these 3 years more than $150 million was invested in new plant and equipment, which was more than half of the total investment made in new plant and equipment in the industry, from the time it came into being through 1956.

Factors Affecting the Demand for Antibiotics

Although new and important uses have been developed for antibiotics in the fields of animal feed and agriculture, by far the greatest demand for antibiotics is for medicinal use in the treatment of human diseases. The present chapter is primarily concerned with antibiotics produced and sold as prescription drugs. The analysis which follows

is therefore inapplicable to those antibiotics which are not widely used for prescription purposes, such as bacitracin, neomycin, and tyrothricin.

Several important factors affecting the demand for antibiotics for prescription uses are to be noted. One is that the total demand is determined by the incidence of illnesses which can be effectively treated with them. Therefore, to the extent that their use reduces the number of cases to be treated, the potential demand for them is reduced. In other words, any preventive effect that their use may have is a built-in limitation on the demand for them. A second factor is that the patient seldom exercises any choice in selecting an antibiotic since only a few insignificant antibiotic preparations can be bought without a doctor's prescription. The doctor's selection based on his judgment as to which of several antibiotics may be the most effective treatment for a given illness becomes the controlling demand factor. Therefore, among manufacturers one aspect of competition is the effort to obtain the doctor's acceptance of their respective antibiotic products.

Furthermore, when health and life are at stake, price is at most only a minor consideration to the physician prescribing the drug. Thus, the patient's need and not the price, plus the incidence of particular diseases and the expert knowledge of all physicians as to which antibiotic is most effective in treating each particular case, are all factors determining the demand for a particular antibiotic. It may therefore be said that the total demand for a particular antibiotic is not directly related to changes in its price.

Where a particular antibiotic is manufactured and marketed by several companies in standardized dosage forms, each company's share in the market for that particular antibiotic dosage form may well depend in part upon each company's price for that particular product. Also, where products are closely substitutable each company's share in the market may depend to some degree upon the price it charges for its own particular product. In such situations the price charged by a particular company may influence the demand by physicians, wholesalers, hospitals, and retailers for that company's product.

The reputation of a drug company and its brand name may outweigh price as a consideration in the physician's choice. Being aware of the physician's responsibility in selecting from among several antibiotics, the companies marketing antibiotics spare no effort in disseminating information to the medical profession as to the clinical effectiveness of their particular antibiotics. Clinical study by producers, and passing information on to physicians through visitation by detail men, the giving of samples, advertising in medical journals and through direct mail become highly important in promoting the

sale and use of antibiotics. Where particular antibiotics, for example, tetracycline, erythromycin, and novobiocin, are sold by two or more manufacturers, each seller concentrates his efforts on promoting his particular trademark or trade name for that product directly to the medical profession and to the drug trade.

Still another factor affecting both the discovery and subsequent production and distribution of new antibiotics is that the development of each new substance is the result of laboratory research followed by clinical evaluation of the effectiveness of the new substance. Regardless of whether such preliminary expenditures of time and money may be large or small, they must be made before beginning volume production and the development of the market (through dissemination of clinical results, detailing, distribution of free samples), and before the establishment of distributor and retailer stocks upon which physicians can draw by prescription.[4] Also, the manufacturer who is already marketing one or more older antibiotics must undertake market development for each new one with the knowledge that, if the new substance is more effective for some purposes than the old one, its introduction may reduce the demand for the older one. This competition of the manufacturer with himself, as well as with others, through the substitution in use of a new for an old product often is very real. A mitigating factor, however, is that the fermentation processes by which most antibiotics are produced are so similar that the manufacturing equipment used is largely interchangeable in the production of different antibiotic substances.

The Marketing System and Antibiotic Prices

Marketing functions

In 1956 there were 12 companies producing bulk antibiotics in large quantities.[5] Considerable quantities of these bulk materials are packaged in dosage forms by the original manufacturers. These dosage forms may either be labeled and distributed under the producer's own trademark or trade name, or they may be sold without such trade identification to other companies which place their own

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[4] In addition, all new drugs must be approved by the Food and Drug Administration prior to their sale in interstate commerce. This approval should be distinguished from the certification of antibiotics to the Food and Drug Administration. Certification procedures apply to the manufacturers' output of certain specified antibiotics. Each certification means examination by the Food and Drug Administration of each batch of the antibiotic produced for identity, strength, quality, and purity before such batch is shipped in interstate commerce. Baron, Handbook of Antibiotics, Reinhold Publishing Corp., New York, 1950, p. 8.

[5] These companies in alphabetical order are Abbott Laboratories, American Cyanamid Company, American Home Products Corporation, Bristol-Myers Company, Commercial Solvents Corporation, Eli Lilly and Company, Merck & Co., Inc., Olin Mathieson Chemical Corporation, Parke, Davis & Company, S. B. Penick & Company, Chas. Pfizer & Co., Inc., and The Upjohn Company.

labels on the packages and distribute the products so packaged. Bulk materials of medicinal grade are generally sold to packagers and compounders, some of which are also manufacturers of antibiotics themselves. Others merely package and distribute the products under their own labels.

The packaging and labeling practices relating to several antibiotics considered in this chapter differ in some respects from those described above. Of the broad spectrum antibiotics, for example, three are patented products each of which is manufactured by a single company that sells all of its production under its own labels. These antibiotics are Aureomycin, produced only by American Cyanamid; Terramycin, produced only by Pfizer; and Chloromycetin, produced exclusively by Parke, Davis. The fourth is tetracyline, which is produced by American Cyanamid, Pfizer, and Bristol and is sold in bulk [6] to two purchasers only: Olin Mathieson and Upjohn. Bulk sales of antibiotics for medicinal purposes, therefore, are made principally in the distribution of the penicillins, streptomycin, and dihydrostreptomycin.

A further difference has to do with antibiotics of animal feed or other nonmedicinal grades that are sold in bulk to producers of animal feeds, food preservatives, insect sprays, etc. These products generally do not enter into the same distribution channels through which antibiotics of medicinal grade for human use are distributed.

Chart 7 shows the channels through which antibiotics of medicinal grades may move, either in bulk or in dosage forms.

As the solid black lines on the chart indicate, finished dosage forms of antibiotics may be sold by the original manufacturers, or by the compounders and finishers, either to wholesalers, or directly to retailers, or directly to hospitals and physicians. Retailers likewise may sell to hospitals and physicians or direct to patients on prescription. Doctors may dispense or administer directly to patients either in or out of hospitals, or they may give nonhospitalized patients a prescription which the patient presents to the retailer. Of the two major categories of dosage forms—for injection or for oral administration—the former is usually dispensed by the physician or hospital, whereas the latter, as tablet, capsule, or oral suspension, is normally purchased from the druggist upon presentation by the patient of the physician's prescription.

Bulk term purchase and distributor contracts

As shown in chart 7, some antibiotics are sold in bulk by the original manufacturer to compounders and packagers and to other manufacturers which in this instance function as compounders or packagers. Some of these bulk sales have been made pursuant to term

[6] The term "bulk," as used in this chapter, includes unlabeled dosage forms.

Principal Antibiotic Marketing Channels

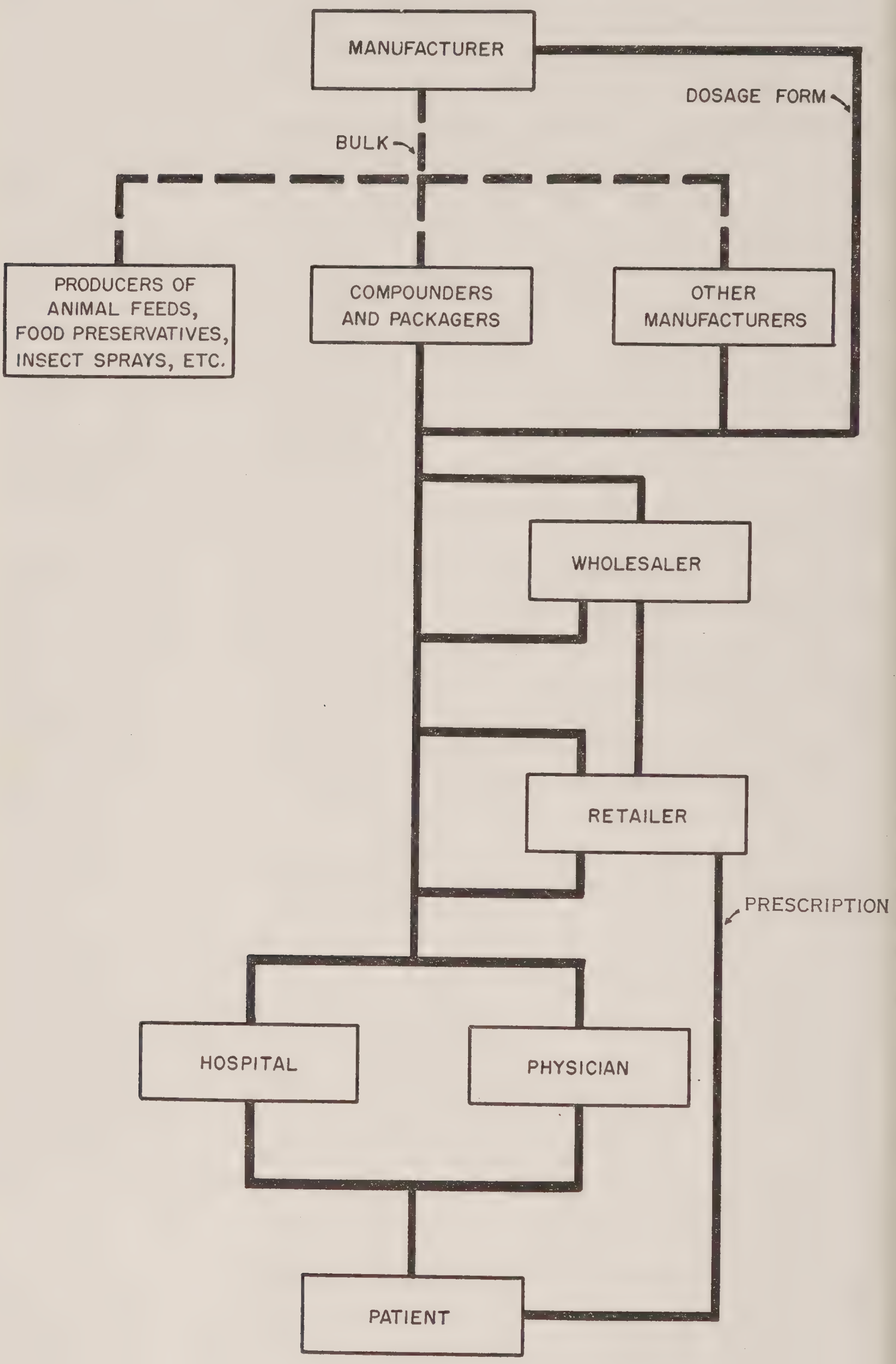

CHART 7.

purchase contracts. The percentage of total antibiotic bulk sales which moves under such contracts is not known, but there is reason to believe that it is not large.

Such term purchase contracts were part of the pharmaceutical industry before the advent of antibiotics. Until 1949, the sellers under the term purchase contracts for antibiotics of which the Federal Trade Commission has record were manufacturing chemists. They supplied pharmaceutical houses, but did not sell dosage forms under their own labels. Beginning in 1949, however, some pharmaceutical houses sold bulk-packaged and unlabeled penicillin and streptomycin dosage forms to other pharmaceutical houses and packagers while continuing to distribute the same antibiotics under their own labels. In addition, Pfizer, formerly a manufacturing chemist only, began in 1950 to distribute antibiotic dosage forms under its own label. Both these developments put these sellers in the position of offering their products at the same levels of sale as those their customers were serving.

Term purchase contracts have taken several forms. Some of them have been tied either to the buyer's total requirements or his purchase requirements. Others have provided for minimum and maximum quantities of specified antibiotics for a specified period. The data furnished to the Commission indicate that prices for antibiotics sold under these agreements were considerably less than the published prices at which the manufacturers offered the same products in bulk.

For example, one of the largest manufacturers of penicillin offered unlabeled vials containing 400,000 units of a combination of procaine and potassium penicillin on March 31, 1954, for sale at the following quantity differentials:

Quantity differentials (vials):	*Percent of 400-vial price*
400	100. 0
1,000	96. 5
5,000	94. 3
10,000	92. 1
25,000	87. 7
50,000	83. 3
100,000	78. 9

On June 1, 1954, when the prices yielding the above quantity differentials were still in effect, this supplier made a term contract to supply the same penicillin combination in the same vial size (also unlabeled) to another antibiotics manufacturer for a price equivalent to 56.1 percent of the 400-vial price.

The older penicillins and the streptomycins have also been sold under "distributor" agreements. An agreement relative to unlabeled dosage forms of the streptomycins which was entered into in January

1950 and which was effective at least until August 1957 may be used to illustrate this type of term purchase.

The "distributor" was named a "nonexclusive selling agent" of the manufacturer. It was specified that title to the dosage forms received by the distributor would remain with the manufacturer until they were sold. The distributor agreed to pay all expenses of labeling and further packaging, in addition to all selling and promotional costs. The initial "consignment billing prices" (the prices of different dosage forms charged to retailers and hospitals) were specified, as was the initial "percentage commission" to the distributor, which he deducted before remitting the sales proceeds to the manufacturer. If the published trade price of the principal competitors of the supplier should fall below the consignment billing price, there were provisions looking to adjustment of both the consignment billing price and the rate of the distributor's commission. But it was also provided that "* * * the consignment billing prices shown on the attached schedule shall not be reduced without the consent of * * * [the supplier]." The supplier thus reserved the right to name the price at which the selling agent would offer, under the agent's labels and trade names, products whose ingredients were identical with those which the supplier also was offering under its own labels and trade names.

In table 41, the initial consignment billing price for the 1-gram vial of either streptomycin or dihydrostreptomycin sulfate, the net price to distributor, and the rate of commission are shown opposite the date, February 1, 1950, on which the agreement became effective. Thereafter, each effective date of change was specified in a letter from the manufacturer to the distributor. Each of these letters set forth the "consignment billing price," the "distributor's commission," and the "net price." The column giving the amount of the distributor's commission has been added for convenience.

TABLE 41.—*Consignment billing price and net price of streptomycin or dihydrostreptomycin sulfate under distributor agreement of Jan. 10, 1950: Feb. 1, 1950, to Nov. 1, 1954*

[Prices are per 1-gram vial]

Effective date	Consignment billing price [1]	Net price to distributor	Distributor's commission	
			Percent	Amount
Feb. 1, 1950	$0.60	$0.315	47.5	$0.285
Mar. 12, 1952	.40	.27	32.5	.13
May 1, 1952	.40	.24	40.0	.16
Nov. 1, 1952	.40	.21	47.5	.19
Dec. 1, 1952	.40	.20	50.0	.20
Jan. 1, 1953	.36	.1998	44.5	.1602
Apr. 1, 1954	.36	.18	50.0	.18
July 1, 1954	.36	.1494	58.5	.2106
Nov. 1, 1954	.36	.12996	63.9	.23004

[1] Price charged retailers and private hospitals for vials bearing the distributor's label.

Source: FTC data request, 1957.

Price to retailers, to hospitals, and the public

Original manufacturers selling antibiotics directly to retailers and hospitals usually price their products on the basis of a general formula. Essentially, this formula is 40 percent less than the "list" price of the antibiotics, whatever that list price may happen to be. "List" price is the price which the manufacturer suggests to the retailer as the price to be charged to the consumer. Assuming 100 to be the "list" price of a product, the manufacturer's price to the retailer would be 60. The list prices of the different antibiotics vary widely, those of the older penicillins and streptomycins being lower than those of the broad spectrums and the newer penicillin specialties. The application of the 40-percent trade discount off the suggested retail list price causes the two classes of antibiotics to reach retailers and hospitals at correspondingly different prices. Since retail and wholesale margins are based upon rather standard percentage markups, it follows that lower priced items produce lower retail and wholesale dollar margins than the higher priced items do. For antibiotics, the fair trade minimum retail price fixed by producers is almost invariably 10 percent less than the retail "list" price; i. e., 90 percent of the manufacturer's suggested retail price for each antibiotic item.

Price to the wholesaler

Prices quoted by original manufacturers to wholesalers differ from those charged by original manufacturers to retailers. As noted above, a single formula is applied by most original manufacturers who sell antibiotic dosage forms directly to retailers. However, the pricing of antibiotics sold by original manufacturers to wholesalers is *not* controlled by such a single formula.

Taking 60 as the uniform price at which antibiotics are sold directly to retailers by original manufacturers, the prices to wholesalers vary between 47.4 and 51. If the wholesaler obtains the antibiotic from the original manufacturer at a price of 47.4, and sells to the retailer at a price of 60, then the wholesaler's gross profit margin is 21.0 percent of the price at which he sells to the retailer. If, on the other hand, the wholesaler pays a price of 51 to the original manufacturer, and sells to the retailer at a price of 60, the wholesaler's margin is 15.0 percent. At least one manufacturer of antibiotics sells only to wholesalers, while another manufacturer reported that it sells only to retailers. Other manufacturers of antibiotics sell to both wholesalers and retailers. Thus, to the extent that such manufacturers sell to retailers, they perform the wholesale function themselves. One manufacturer reports that it does not sell directly to physicians.

The function performed by the independent wholesaler is of particular value to the small, independent retailer. There are literally

hundreds of different antibiotic preparations marketed; often the same preparation is sold under 10 or more different trademarks or trade names. Under such circumstances it would be a heavy burden on the capital resources of the small retailer if he had to maintain a large inventory of many infrequently prescribed articles. The wholesaler can, to a considerable extent, relieve the retailer of this burden by stocking such items and delivering them to the retailer as needed by him.

Additional discounts to wholesalers, retailers, and hospitals

In addition to the selling prices quoted by manufacturers to wholesalers, retailers, and hospitals, various types of discounts may be applied on sales by the manufacturer to certain classes of his wholesale and retail customers. These include both quantity discounts and cash discounts.

In addition to the standard discount of 40 percent to retailers and hospitals, manufacturers grant further special discounts depending upon the total dollar purchases. For example, on orders aggregating $500, Parke, Davis & Co. permits an additional discount of 8 percent. Retailers receive another 4-percent discount on all purchases over $4,000 per year, while hospitals are granted this 4-percent discount on all orders.[7]

Cyanamid allows to retailers and hospitals a 7½-percent reduction over and above the 40-percent trade discount on all orders between $50 and $100. On orders exceeding $100, the additional discount is 15 percent. However, no additional discount is granted by Cyanamid on any Aureomycin and Achromycin sales.[8]

Apart from these quantity discounts for volume and size of orders, it is customary in the antibiotics industry for manufacturers to allow a 2-percent discount for cash payment before the 10th of the month following delivery to the purchaser. This discount is extended to all classes of purchasers. Unless the customer requires shipment by a special form of transportation, such as air express, transportation charges are normally paid by the seller, i. e., the manufacturer, except on very small orders.

Where private hospitals place their orders for antibiotics through wholesalers or retailers, it is a fairly general practice among the antibiotics companies to allow a 10-percent discount to the wholesaler or retailer, where the manufacturer ships directly to the hospitals.

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[7] John D. McEvilla, "Competition in American Pharmaceutical Industry," Ph.D. thesis, University of Pittsburgh, 1957, appendix F, p. 184.
[8] FTC data requests, 1956, 1957.

Special credits available to customers

Antibiotic dosage forms lose potency in storage. Upon completion of their manufacture they are stamped with an "expiration date"; after this date they are considered not to meet the potency standards under which they were issued. It is customary for the manufacturers to allow full credit at current prices for "expired" antibiotic dosage forms returned by their customers in unbroken, undamaged, original packages. Some manufacturers also guarantee customers' floor stocks of antibiotic dosage forms against price decline—at least for a stated period after the date of purchase. The difference between cost and the value of inventories at reduced prices is allowed to customers as a credit.

Sometimes local and State governmental institutions are given a special discount not available to private hospitals. Prices to Federal Government agencies are discussed in subsequent sections of this chapter.

Free goods in the antibiotics industry

In keeping with a longstanding practice in the pharmaceutical industry, producers of antibiotics have, in the past, made offers to supply certain classes of purchasers of particular antibiotics dosage forms with additional amounts of such dosage forms without charge. This is referred to as the giving of "free goods," and is usually resorted to only in times of competitive stress.[9] What it amounts to, in effect, is a lowering of the unit price of the commodity being sold without reducing the "official" price. In view of this practice, prices listed in the tables appearing below may have been considerably higher than actual prices during certain periods of time.

For example, one manufacturer issued in years past price lists which show that on purchases of specified quantities of penicillin and streptomycin dosage forms additional amounts of such products were delivered to the purchaser without charge. Thus, on orders for 100 vials of a given penicillin, streptomycin or dihydrostreptomycin product, the manufacturer shipped an additional 50 vials without charge.

While actual dosage form prices were considerably lower than those specified in company price lists whenever free goods were added to shipments, the price tables which follow, although based on such lists, nevertheless clearly demonstrate the price trends of important penicillin and streptomycin dosage forms. No data are available which

[9] "Free goods" should be distinguished from the free samples distributed to physicians by pharmaceutical manufacturers.

would suggest that the free-goods practice was also employed in connection with the distribution of dosage forms of broad spectrum antibiotics.

Price Histories of Selected Antibiotics

In foregoing sections of this chapter, consideration has been given to significant factors affecting antibiotic prices. In succeeding sections the price histories of the penicillins, the streptomycins, and the broad spectrum antibiotics will be presented.

Price history of selected penicillin products

Penicillin bulk prices.—Bulk penicillin was commercially introduced in 1945 as sodium penicillin in amorphous form. In early 1947 this salt of penicillin was made available in the more refined crystalline form. As shown by table 42 below, in 1948, two additional salts of bulk penicillin were offered: potassium and procaine penicillin. These penicillin salts are merely representative of other penicillin products sold in bulk. There appears to be little distinction in prices among the various bulk penicillins. Indeed, one penicillin manufacturer (Lilly) offered several different bulk penicillin products at one uniform price which varied with respect to the quantities sold.

Listed in table 42 are bulk sodium, potassium, and procaine penicillin prices for selected manufacturers from 1945 to 1956. Bulk sodium penicillin prices of Merck & Co. are presented in column I; bulk potassium penicillin prices of Bristol are specified in column II; in column III are listed Pfizer's bulk procaine penicillin prices; and column IV contains prices of potassium or procaine salts of bulk penicillin sold by Eli Lilly & Co.

Three conclusions may be drawn from the data presented in table 42; first, bulk penicillin prices fell from $6,000 per billion units for Merck's amorphous sodium salt in 1945 to $34.50 per billion units of Bristol's potassium salt in 1955, or about one-half of one percent of the introductory price of amorphous sodium penicillin, the production of which was discontinued when penicillin products of greater purity were developed. Second, a reduction in the bulk price of one salt of penicillin was usually matched or approximated by price reductions in the other salts of penicillin. Third, the prices of the various salts of penicillin named in table 42 have tended to be about the same at any particular time over the 12-year period. The wide gaps between successive catalog prices, for example the decline from $800 to $330 per billion units for Lilly's bulk penicillin between November 1948 and November 1949, suggests that actual prices of all penicillin bulk products listed in the table may have been more nearly uniform than would appear from published quotations.

The history of penicillin bulk prices demonstrates the effect of increasingly efficient production techniques (which implies decreasing unit cost of production) linked with persisting competitive pressures. Thus, within a few years' span, 1945 to 1948, bulk prices per billion units fell from $6,000 to a range of $800 to $900. Between 1949 and 1952 prices dropped from about $750 to a low of $85. During 1953, 1954, and 1955 these prices declined further, reaching their lowest level in December 1955, when one manufacturer (Bristol) offered bulk penicillin at $34.50 and another producer (Lilly) quoted both potassium and procaine salts of penicillin at $35 per billion units. In 1956, bulk prices increased from the level of about $35 to a high of $63.50 for sodium penicillin in November 1956.

Notwithstanding the 1956 price increase and even though the Federal Trade Commission is not in possession of cost data as to *unit* costs of production, the following observation would seem to be justified: for the period 1945 to 1955, declining costs of production and vast increases in productive capacity have made possible reductions in prices of these products. Further pressure on penicillin prices after 1949 resulted from inroads of competing, newly discovered antibiotics, such as the broad spectrums. Competition among manufacturers of bulk penicillin was the mechanism through which the benefits resulting from decreasing cost of production were passed on to the purchasers.

From the medical aspect, there may be varying advantages in administering a particular salt of penicillin in a particular case. However, insofar as bulk prices of penicillin are concerned, table 42 shows that there was hardly any difference in price among the various salts of penicillin named. For example, in 1948, sodium, potassium, and procaine penicillin were offered in bulk at about the same price, $900 per billion units, by three manufacturers (Merck, Bristol, and Pfizer). A fourth manufacturer (Lilly) quoted several products containing potassium or procaine salts of bulk penicillin at a single lower price; namely, $800 per billion units for each. In January 1952, the bulk prices for sodium and procaine penicillin ranged from $250 to $300, while the bulk price for potassium penicillin was quoted at $250 per billion units.

The effect of a reduction in price of one salt of bulk penicillin on prices of the other salts of bulk penicillin may be illustrated by the following: In July 1949, one manufacturer (Pfizer) quoted a bulk price of $525 per billion units of procaine penicillin. In August of 1949, another manufacturer (Merck) reduced its price for sodium penicillin to $525 per billion units, while a third producer (Bristol) offered potassium at $400. In December 1952, potassium penicillin was quoted at $100 by Bristol, whereas Lilly offered two salts of bulk

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TABLE 42.—*Penicillin bulk prices: 1945–56*

[Prices [1] in dollars per billion units (BU)]

Month	Year	Sodium penicillin (Merck)		Potassium penicillin (Bristol)	Procaine penicillin (Pfizer)	Procaine or protassium penicillin (Lilly) [2]
		Amorphous	Crystalline			
May	1945	6,000.00				
May	1946	3,600.00				
January	1947	2,100.00	2,500.00			
May	1948	1,450.00				
July	1948		1,250.00	1,300.00	1,300.00	
November	1948					800.00.
December	1948		900.00	900.00	950.00 (2.5–9 BU)	
					925.00 (10–24 BU)	
					900.00 (25 BU or more)	
March	1949		700.00		750.00 (2.5–10 BU)	
					725.00 (10–24 BU)	
					700.00 (25 BU or more)	
July	1949		575.00		575.00 (5–9 BU)	
					550.00 (10–24 BU)	
					525.00 (25 BU or more)	
August	1949		525.00	400.00		
November	1949					330.00.
						300.00.
January	1950		450.00	350.00	475.00 (less than 25 BU)	
					450.00 (25 BU or more)	
March	1950			300.00		
August	1951				375.00 (less than 100 BU)	250.00.
					350.00 (100 BU or more)	
January	1952		300.00 (less than 5 BU)	250.00	300.00 (less than 25 BU)	
			270.00 (5 to 24 BU)		275.00 (25–99 BU)	
			250.00 (25 or more BU)		250.00 (100 BU or more)	
February	1952			225.00		
March	1952			200.00		
April	1952			150.00		
June	1952				200.00 (less than 25 BU)	
					175.00 (25–99 BU)	
					150.00 (100 BU or more)	
September	1952			125.00		
December	1952			100.00	95.00 (less than 100 BU)	115.00.
					85.00 (100 BU or more)	
January	1953		90.00 (less than 100 BU)		90.00 (less than 100 BU)	120.00.
			85.00 (100 BU or more)		85.00 (100 BU or more)	
February	1953					95.00.
March	1953			85.00		

October	1953					90.00.
December	1953			80.00		
January	1954					85.00 (less than 100 BU). 80.00 (100 BU or more).
June	1954		80.00 (less than 100 BU) 75.00 (100 BU or more)	70.00	80.00 (less than 50 BU) 75.00 (50 BU or more)	75.00 (less than 100 BU). 70.00 (100 BU or more).
September	1954			61.50 55.00		
November	1954				57.50 (less than 50 BU) 55.00 (50 BU or more)	60.00.
December	1954			54.00		50.00 (less than 25 BU). 47.00 (25-49 BU). 45.00 (50-99 BU). 44.00 (100-249 BU). 42.00 (250-499 BU). 40.00 (500 BU or more).
April	1955			52.25		
May	1955		55.00			
June	1955			42.50		
July	1955					44.00 (1-9 BU). 42.00 (10-19 BU). 40.00 (20-49 BU). 38.00 (50-199 BU). 37.50 (200-499 BU). 36.00 (500-999 BU). 35.00 (1,000 BU or more). (Prices in effect until Jan. 1, 1956.)
September	1955			37.50		
October	1955			36.50		
December	1955			34.50		
April	1956				52.00 (less than 50 BU) 50.50 (50-99 BU) 49.00 (100-249 BU) 47.50 (250 BU or more)	
June	1956		51.00 (less than 50 BU) 50.00 (50 BU or more)	46.00 [3] 45.00		
August	1956		56.00 (less than 50 BU) 55.00 (50 BU or more)	48.50 [3] 47.50		
October	1956				57.50 (less than 50 BU) 52.50 (50 BU or more)	
November	1956		63.50 (less than 50 BU) 62.50 (50 BU or more)	 57.50		

[1] Prices for Merck, Pfizer, and Lilly are taken from catalog prices; those for Bristol are actual prices at which sales were made.
[2] Lilly's bulk price for 1956 not available.
[3] 50 BU or more.

Source: FTC data requests, 1956 and 1957.

penicillin at $115 per billion units. During approximately the same period, one manufacturer of procaine penicillin (Pfizer) reduced the bulk price for this product in December 1952 to $95 and $85 per billion units, depending upon quantities purchased. By June 1954 there were further reductions by all four manufacturers as a result of which the bulk prices for the three salts of penicillin were reduced to $80, $75, and $70, again depending upon the quantities purchased.

Certain qualifying observations should be made in concluding this discussion of bulk penicillin prices. The price data contained in table 42, while based upon reports by the various companies to the Federal Trade Commission, may be in some instances mere approximations of the actual bulk penicillin prices at certain times. Several important factors are not reflected in these price data. One of these is the effect of term contractual arrangements between certain suppliers and certain purchasers under which more favorable prices have been offered on large quantity purchases over specified periods of time. Discounts, credits, and the existence of differing price offers to differing classes of purchasers affect the actual price per unit of bulk penicillin.

It should not be inferred that the four companies selected for discussion in table 42 sell or have sold only the particular penicillin products in bulk which are identified with these companies in this table. Merck, for example, has sold potassium and procaine penicillin, as well as sodium penicillin, during most of the time period under discussion. Many more price changes were reported by Merck for potassium and procaine penicillin than for sodium penicillin. Merck's sodium penicillin bulk prices are presented and discussed merely for the purpose of illustrating the great price declines which occurred between 1945 and 1956, and to indicate the manner in which prices of the three penicillin salts have tended to be at about the same level at any particular time.

The data in table 42 demonstrates general downward price movements by which the price levels of bulk penicillin were drastically reduced during the years 1945–56.

Prices of penicillin in dosage forms.—Penicillin dosage form prices fell sharply from the original price of about $20 per vial of 100,000 units in 1943 when only very small quantities of penicillin could be produced. By August 1945, when greatly advanced production techniques had come into use, it was reported that the price of penicillin was "well below $1 per vial" of 100,000 units and further, that many large purchasers were buying at prices "below current market quotations." [10] By 1947 the 100,000-unit vial was being sold to retailers at a price of about $0.29 or $0.30 per vial, and vials containing 1 million

[10] Memorandum dated October 30, 1945, from Lawrence Brown, Assistant Director of the Chemicals Bureau, War Production Board.

units of potassium penicillin were priced at approximately $2.40 to retailers late in 1947. Prices continued at this level through 1948.

In 1948, procaine penicillin was introduced, and quickly became the most widely used type of penicillin. Many of the original introductory dosage forms of procaine penicillin, as for example, the 3-million unit vial in aqueous suspension, have remained in use up to the present writing. Therefore, the 3-million unit vial of procaine penicillin has been selected to illustrate, in a detailed presentation, the course of penicillin dosage form prices to retailers and to hospitals from 1948 through 1956.

The following analysis is confined to procaine penicillin price *trends* during the period of discussion. One reason why the analysis must be considered as relating solely to the trend of prices during the years 1948–56 is that the original manufacturers replying to the Federal Trade Commission's 1956 data request indicated that at particular times, competition in the sale of procaine penicillin dosage forms has been such that actual prices charged differed from published prices. Therefore, price changes, as they appear in table 43 and as discussed in the text, tend to lag behind actual company prices during particular periods. Thus, no comparisons are intended among the various companies' *actual* prices at any particular time.

The introduction of procaine penicillin in 1948 was of major importance since this form of penicillin remained active in the bloodstream for much longer periods than any other form of penicillin known at that time. In order to illustrate the course of procaine penicillin prices from 1948 through 1956, prices quoted during these years by four sellers of these products—Abbott Laboratories, Bristol Laboratories, Chas. Pfizer & Co., Inc., and Wyeth Laboratories—are presented in table 43.

Three separate dosage forms containing 3 million units (10 doses) of procaine penicillin which have been offered at various times by one or more of the four companies listed in table 43 will be used to illustrate price trends in this period. These dosage forms are: (1) procaine penicillin in oil; (2) procaine penicillin in oil with 2 percent aluminum monostearate; (3) procaine penicillin in aqueous suspension. During the years 1948–56, all three dosage forms were at certain times offered to retailers at an identical price per 3 million units. At other times, price differentials have appeared among the three dosage forms.

Of the 4 companies chosen for this presentation, Abbott was the first to introduce procaine penicillin in oil, in the 10-dose, 3-million-unit vial, offering the product to retailers in February 1948 at a price of $10. In October 1948, Abbott lowered the price by 20 percent, to $8. In the same month, Bristol marketed 3 million units

TABLE 43.—*Procaine penicillin dosage form prices of 4 sellers: 1948–56*

[3-million unit, 10-dose vial, in oil, in oil with 2 percent aluminum monostearate, and in aqueous suspension]

Month	Year	Abbott Laboratories						Bristol Laboratories				Chas. Pfizer & Co., Inc.[1]				Wyeth Laboratories			
		In oil		In oil w/2% alum. mono.		In aqueous suspension		In oil w/2% alum. mono.		In aqueous suspension		In oil w/2% alum. mono.		In aqueous suspension		In oil		In aqueous suspension	
		List	Price to retailer	List	Price to retailer	List	Price to retailer	List	Price to retailer	List	Price to retailer	List	Price to retailer	List	Price to retailer	List	Price to retailer	List	Price to retailer
February	1948	$16.67	$10.00	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------	------
October	1948	13.34	8.00	------	------	------	------	[2] $16.67	$10.00	------	------	------	------	------	------	------	------	------	------
March	1949	10.00	6.00	$10.00	$6.00	------	------	10.00	6.00	------	------	------	------	------	------	------	$6.00	------	------
June	1949	7.50	4.50	7.50	4.50	------	------	6.98	4.19	------	------	------	------	------	------	------	4.50	------	------
December	1949	5.42	3.25	5.42	3.25	------	------	------	2.00	------	$3.56	------	------	------	------	------	4.50	------	------
March	1950	5.42	3.25	5.42	3.25	------	------	------	1.78	------	2.60	------	------	------	------	------	2.00	------	$3.25
April	1950	5.42	3.25	5.42	3.25	$5.42	$3.25	------	2.23	------	3.25	------	$2.60	------	$3.25	------	2.00	------	3.25
August	1950	5.42	3.25	5.42	3.25	5.42	3.25	5.42	3.25	$5.42	3.25	$4.34	2.60	$5.42	3.25	------	2.50	------	3.25
January	1952	(3)	(3)	3.34	2.00	3.75	2.25	4.17	2.50	5.42	3.25	4.34	2.60	5.42	3.25	------	2.25	------	2.25
March	1952	------	------	2.33	1.40	2.33	1.40	4.17	2.50	------	3.25	2.33	1.40	2.33	1.40	------	1.80	------	1.80
April	1952	------	------	2.33	1.40	2.33	1.40	2.34	1.40	2.34	1.40	2.33	1.40	2.33	1.40	------	1.56	------	1.56
January	1953	------	------	1.73	1.04	1.73	1.04	2.34	1.40	2.34	1.40	2.33	1.40	2.33	1.40	------	1.21	------	1.00
February	1953	------	------	1.73	1.04	1.73	1.04	2.34	1.40	2.34	1.40	1.73	1.04	1.73	1.04	------	1.21	------	1.00
April	1953	------	------	1.73	1.04	1.73	1.04	1.73	1.04	1.73	1.04	1.73	1.04	1.73	1.04	------	1.00	------	1.00
July	1953	------	------	1.73	1.04	1.73	1.04	1.73	1.04	1.73	1.04	1.73	1.04	1.73	1.04	------	1.04	------	1.04
October	1954	------	------	1.34	.80	1.34	.80	1.73	1.04	1.73	1.04	1.73	1.04	1.73	1.04	------	1.04	------	1.04
December	1954	------	------	1.34	.80	1.34	.80	1.73	1.04	1.73	1.04	1.73	1.04	1.73	1.04	------	.80	------	.80
April	1955	------	------	1.34	.80	1.34	.80	1.73	1.04	1.73	1.04	1.34	.80	1.34	.80	------	.80	------	.80
May	1955	------	------	1.00	.60	.94	.56	1.73	1.04	1.73	1.04	1.34	.80	1.34	.80	------	.80	------	.80
June	1955	------	------	1.00	.60	.94	.56	1.73	1.04	1.73	1.04	1.34	.80	1.34	.80	------	.66	------	.56
April	1956	------	------	1.00	.60	.94	.56	.94	.56	.94	.56	1.10	.66	.94	.56	------	[5] .56	------	.56
December	1956	------	------	[4] 1.00	[4] .60	.94	.56	.94	.56	.94	.56	1.10	.66	.94	.56	------	[5] .56	------	.56

[1] Prior to Apr. 1, 1950, Chas. Pfizer & Co., Inc., did not sell to the drug trade and to physicians under its own label.
[2] Reduced to $13.34 effective Oct. 16, 1948.
[3] Dosage form discontinued October 1951.
[4] Prices taken from the American Druggist Blue Book, 1956–57.
[5] Wyeth's price lists for 1956, as submitted to the Federal Trade Commission, described this product as containing 2% aluminum monostearate. Wyeth's price filings for 1948–55, did not indicate that the product contained aluminum monosterate.

Source: FTC data requests, 1956, 1957.

of procaine penicillin in oil with 2 percent aluminum monostearate, at a published price of $10. Still later in October 1948, Bristol reduced its price to $8, matching Abbott's October reduction. By March 1949 both companies were offering both dosage forms for $6, and by this time Wyeth had entered the market. It was selling 3 million units of procaine penicillin in oil at $6, the same price as that quoted by Abbott and Bristol.

Another price reduction had occurred by June 1949. Bristol was selling the aluminum monostearate dosage form for $4.19; Abbott and Wyeth, however, were listing the product at $4.50; Abbott offered both the aluminum monostearate form, and the product in oil without aluminum monostearate to retailers at the same price, namely $4.50. Wider disparities in list prices appeared by December 1949. Wyeth continued to maintain a $4.50 price while Abbott reduced its price for both dosage forms (in oil and in oil with aluminum monostearate) to $3.25.

Bristol was the first of the companies chosen for this presentation to market procaine penicillin in aqueous suspension, offering this particular dosage form at $3.56 to retailers in December 1949. Bristol's price for the aluminum monostearate form had been reduced to $2 in the same month, marking its lowest published price for procaine penicillin since the product was introduced in 1948.

Early in 1950 Abbott introduced procaine penicillin in aqueous suspension, listing the dosage form to retailers at $3.25. Abbott's published price for both the aqueous suspension and the aluminum monostearate dosage forms remained at this level through the remainder of 1950 and during the entire year 1951. Thereafter, Abbott discontinued the dosage form in oil.

Meanwhile, in March 1950, Bristol reduced its published prices to retailers for procaine penicillin in aqueous suspension from $3.50 to $2.60, and for aluminum monostearate from $2 to $1.78. Wyeth's prices in March 1950 were $3.25 for aqueous suspension and $2 for procaine penicillin in oil. There was thus considerable variation in prices at which each of the three sellers—Abbott, Bristol, and Wyeth—were offering the same dosage forms.

In April 1950 Pfizer entered the market, selling directly to the drug trade, physicians, and hospitals under the company's own label for the first time. Prior to this date Pfizer sold antibiotics in bulk, including unlabeled dosage forms, but only to other manufacturers and to compounders, packagers, and large wholesalers. This company's first offering of procaine penicillin in oil was at $2.60 to retailers. Pfizer's aqueous suspension dosage form was priced at $3.25, which was the published price being quoted by Abbott, Bristol, and Wyeth to retailers for this dosage form.

Bristol, which as previously noted, had reduced its published price for the aqueous suspension form to $2.60, increased it to $3.25 in April 1950, matching the price charged by Abbott, Bristol, and Wyeth for this dosage form. This price level for aqueous suspension continued until January 1952, when Abbott and Wyeth announced reductions to $2.25.

By April 1952, Abbott, Bristol, and Pfizer had lowered prices for the aqueous suspension form to $1.40. Wyeth's price for this dosage form was quoted as $1.80 in March 1952, and as $1.56 in April of the same year. It is interesting to note that all three dosage forms of procaine penicillin—i. e., in oil, in oil with 2 percent aluminum monostearate, and in aqueous suspension—were selling in April 1952 at the same price, except that Wyeth charged $1.56 for procaine penicillin in oil and in aqueous suspension, compared with $1.40 quoted by the other three companies offering these dosage forms.

Published prices remained the same during the rest of 1952 and until January 1953, when Abbott lowered its prices to $1.04 on both aqueous suspension and oil suspension with 2 percent aluminum monostearate. Wyeth's prices were lowered to $1.21. Pfizer reduced its prices to $1.04 1 month later, February, matching Abbott's prices. In April 1953, Bristol matched Abbott's and Pfizer's price of $1.04. Wyeth, on the other hand, lowered prices to $1 in April, but raised them again to the $1.04 level in July 1953.

These prices continued to be quoted in price listings by all four companies until October 1954, when Abbott reduced prices to $0.80 per 3 million units. This price was met by Wyeth in December 1954. and in April 1955 by Pfizer. According to price filings submitted to the Federal Trade Commission,[11] Bristol Laboratories did not change its quoted price of $1.04 during 1954 or 1955, even though another price reduction was initiated by Abbott in May 1955. In lowering its prices on this occasion, Abbott again opened up a price differential between aqueous suspension and oil with aluminum monostearate dosage forms. This was the first such differential to appear since Wyeth's price charge of April 1953.

Abbott's aqueous suspension price dropped to $0.56; the aluminum monostearate price was reduced to $0.60, however. By June 1955, Wyeth's price for the oil suspension dosage form was quoted at $0.56, the same price quoted for aqueous suspension. The prices were matched by Pfizer in April 1956, and in December of that year, Bristol reduced its price to $0.56 for both oil with aluminum monostearate and aqueous suspension dosage forms. Abbott's prices remained at their 1955 level which, as noted, was $0.56 for aqueous suspension and $0.60 for oil with aluminum monostearate.

[11] FTC data requests, 1956 and 1957.

Based on the data presented in table 43, the following conclusions may be stated. In terms of dollar amounts, the greatest price reduction occurred between February 1948 and December 1949. During this period, the price fell from $10 to $3.25. Thereafter the prices continued to decline steadily until they reached the low point of $0.56 in May 1955. During the remainder of 1955 and in 1956, the price of $0.56 became established as the prevailing price for aqueous suspension, whereas the price for the two oil suspensions varied from $0.56 to $0.66. In percentage terms, the price of 3 million units of procaine penicillin in 1956 was 5.6 percent of the introductory price of $10 for 3 million units of procaine penicillin in oil which had been established in 1948.

Comparative price levels of selected antibiotics

At this time a comparison of price levels among various antibiotics will be undertaken. For this purpose it has been necessary to convert the various antibiotics discussed in this chapter to a standard unit of measure, grams.[12] This necessity arises from the fact that the various types of penicillin are characterized by differing potencies which are measured in units rather than in weight. No comparison of efficiencies among the various antibiotics is intended in making these conversions, since the effectiveness of a particular antibiotic in use depends upon a wide variety of possible circumstances.

The conversions were made on the basis of the theoretical potencies of chemically pure penicillins hereinafter considered. The theoretical potency of each and all of these substances and their respective conversion factors (potency units per milligram of a specified dosage form) have been established by the Food and Drug Administration. Since the theoretical conversion factors have been used in all instances in which a conversion of unit price into gram price has been made, the fact that some dosage forms of antibiotics may be slightly below or slightly above this theoretical potency does not affect, on the whole, the validity of the price per gram comparison. With these qualifications, the following analysis is presented.

As indicated in table 43, 3 million units of procaine penicillin in aqueous suspension were sold to retailers by major manufacturers for about $0.56 in 1956. Since 1 gram of procaine penicillin contains 1,009,000 units theoretical potency,[13] it follows that about 3 grams of procaine penicillin sold for $0.56, or approximately $0.19 per gram, in 1956 in this dosage form.[14]

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[12] The grams used here are measures of antibiotic activity or potency rather than of weights.

[13] Donald C. Grove and William A. Randall, Assay Methods of Antibiotics: A Laboratory Manual, Medical Encyclopedia, Inc., New York, 1955, p. 18.

[14] Here and in the rest of Ch. VI, it must be understood that the manufacturers do not quote or sell these dosage forms on a per-gram basis. Whenever a per-gram price is mentioned, it means that this *would* be the price if the published price were translated into per-gram terms.

The computed prices per gram in 1956 of 5 major manufacturers and of 6 other companies marketing this dosage form under their own labels are listed below:

	Price
Manufacturers:	
Abbott	$0.19
Bristol	.19
Pfizer	.19
Wyeth	.19
Lederle[1]	.31
Packagers:	
Veltex Co	.15
Caprock Pharmacal Co	.17
Lannett Co	.23
S. E. Massengill	.23
Geo. A. Breon & Co	.27
Chase Chemical Co	.45

[1] Although Lederle manufactures certain antibiotics, it is not an original manufacturer of procaine penicillin. In the same manner as the six "packagers," Lederle purchases procaine penicillin in bulk.

Source: American Druggist Blue Book, 1956–57, and FTC data requests, 1956 and 1957.

Of the 12 original manufacturers of antibiotics in 1956, at least 2—Lederle Laboratories and Eli Lilly & Co.—offered procaine penicillin in tablet form. Various compounders and packagers offered this dosage form, of which four—American Drug Products, Lannett Co., Veltex Co., and Vitamix Co.—have been selected for this presentation. Based upon published prices of these 6 companies for their various preparations of procaine penicillin in tablet form in 1956, prices ranged from $0.13 per gram to $0.75 per gram, depending upon the unit content per tablet and the particular company whose product is chosen for computation.

For example, as reference to table 44 will show, Lederle Laboratories' price per gram for procaine penicillin in tablet form may be as high as $0.73 per gram or as low as $0.59, depending upon whether a package containing twelve 50,000-unit tablets is used for computation, or whether a package containing twelve 250,000-unit tablets is selected. One hundred tablets, each containing 50,000 units of procaine penicillin is sold by Lederle at $0.71 per gram, while 100 tablets, each containing 100,000 units of the product, is priced at $0.64 per gram by Lederle. A differential also exists where tablets of equal potency, 50,000 units for example, are sold in packages of varying numbers of such tablets. Twelve tablets of this potency are sold by Lederle at $0.73 per gram, 100-tablet packages are sold at $0.71 per gram, and 500-tablet packages are priced at $0.63 per gram. Differences in packaging and finishing costs probably explain this range of computed prices per gram at least in part, since it seems apparent that it costs more to prepare and label 41 bottles, each containing 12

tablets (or a total of 492 tablets), than to place the same number of tablets into one labeled bottle.

On the other hand, differing packaging costs can hardly account for the price difference shown by table 44, where the same number (100) of the same size tablets (100,000 unit) are offered by various sellers at prices per gram ranging from $0.14 (American Drug Products) to $0.75 (Vitamix).

TABLE 44.—*Computed price per gram of procaine penicillin to retailers: 1956*

[In tablets]

Tablet form	Lederle	American Drug Products	Lannett	Veltex	Vitamix	Lilly [1]
50,000 units:						
12's (0.6 gram)	$0.73				$0.75	$0.62
100's (5 grams)	.71	$0.20		$0.28	[2] .58	.60
500's (25 grams)	.63					
100,000 units:						
12's (1.2 grams)	.68				.63	.58
100's (10 grams)	.64	.16	$0.30	.25	[2] .48	.55
500's (50 grams)	.59		.28			
250,000 units:						
12's (3 grams)	.59				.50	.50
100's (25 grams)		.14	.26	.19	[2] .38	.48
500's (125 grams)			.24			
1000's (250 grams)			.23	.17		

[1] Although Lilly sells only to wholesalers, which resell to retailers, prices of Lilly's procaine penicillin products to retailers are published in Drug Topics Red Book, 1957. These published prices were used in preparation of this table.
[2] The Vitamix Co. offers this product in packages containing 120 tablets. Price computations have been adjusted accordingly.

Source: American Druggist Blue Book, 1956–57; Drug Topics Red Book, 1957 (published fall of 1956); FTC data request, 1957.

There is thus considerable variation in the calculated price per gram of procaine penicillin in tablet form, depending upon the potency of the tablet, the number of tablets per package, and which company's product is selected for purposes of computation. A similar variation exists in the computed price per gram of procaine penicillin sold in suspension. However, the price per gram of procaine penicillin in tablet form is usually somewhat higher than the price per gram of procaine penicillin in aqueous suspension.

An even greater differential existed among prices charged by the various sellers of potassium penicillin, one of the older and much less widely used salts of penicillin.

This particular salt of penicillin is offered in tablet form by most companies engaged in the distribution of antibiotics. The computed prices per gram charged to retailers by Abbott Laboratories, Bristol Laboratories, Merck, Sharp & Dohme, Chas. Pfizer & Co., and Olin Mathieson Chemical Corp., all original manufacturers of antibiotics, are specified in table 45, as are the prices of four additional companies which purchase potassium penicillin in bulk and resell it in dosage

form under their own labels. These four companies are: American Pharmaceutical Co., Evron Co., Raway Pharmacal Co., and Veltex Co.

The price per gram of potassium penicillin varies depending upon unit content of tablets, the number of such tablets per package sold, and the pricing policy of the particular manufacturer whose product is used for determining price per gram. Determinations of price per gram are based upon the following relations: chemically pure potassium penicillin has a potency of 1595 units per milligram, or 1,595,000 units per gram. The gram content of particular tablet dosage forms is determined by multiplying the unit content of individual tablets by the number of such tablets and dividing the sum by 1,595,000 units, the theoretical potency of potassium penicillin. For example, to determine the gram content of 12 tablets, each containing 250,000 units of potassium penicillin, multiply 12×250,000 and divide the sum, 3 million units, by 1,595,000. The result is 1.89 grams. This amount of potassium penicillin is sold to retailers for $1.50 by Abbott Laboratories, or for 79³⁄₁₀ cents per gram. Rounded off, this figure appears in table 45 as $0.79 under Abbott's name. Abbott's price for potassium penicillin per gram runs as high as $0.91 per gram, for 25 tablets, each containing 100,000 units, to as low as $0.59 for 1,000 tablets, each containing 100,000 units.

TABLE 45.—*Computed price per gram of buffered potassium penicillin tablets to retailers: 1956*

Tablet form	Abbott	American Pharmaceutical Co.	Evron Co.	Raway Pharmacal	Veltex Co.	Bristol Laboratories	Merck Sharp & Dohme	Chas. Pfizer & Co., Inc.	Olin Mathieson Chemical Co. (Squibb)
100,000 units:									
Bottle of 25 (1.56 grams)	$0.91	--------	--------	--------	--------	--------	--------	--------	--------
Bottle of 100 (6.26 grams)	.88	$0.49	$0.54	$0.32	$0.51	$0.88	$0.88	$0.88	$0.88
Bottle of 250 (15.67 grams)	.82	--------	--------	--------	--------	--------	--------	--------	--------
Bottle of 1,000 (62.68 grams) (4/250)	.59	--------	--------	--------	.43	.59	--------	--------	--------
250,000 units:									
Bottle of 12 (1.89 grams)	.79	--------	--------	--------	--------	.79	.79	--------	.79
Bottle of 100 (15.67 grams)	.77	.43	.45	.27	.35	.77	.77	.77	.77
500,000 units:									
Bottle of 12 (3.76 grams)	.72	.56	.47	--------	--------	--------	.71	--------	--------
Bottle of 100 (31.35 grams)	.63	.36	.34	.25	--------	--------	--------	.63	--------

Source: American Druggist Blue Book, 1956–57; Drug Topics Red Book, 1957 (published fall of 1956); FTC data request, 1957.

All five of the original manufacturers quoted the same price per gram for each commonly offered dosage form of potassium penicillin in tablet form in 1956. As an example, all five companies charged $0.88 per gram for 100 tablets each containing 100,000 units of po-

tassium penicillin. The four companies which purchased this antibiotic in bulk sold this dosage form to retailers at varying prices per gram. American Pharmaceutical Co. quoted $0.49 per gram, Evron Co., $0.54; Raway Pharmacal Co., $0.32 per gram; and Veltex Co., $0.51 per gram.

A similar pricing situation existed at the conclusion of the time period covered by this report with respect to preparations of 100 tablets, each containing 250,000 units of the product. Abbott, Bristol, Merck, Pfizer, and Olin Mathieson (Squibb) listed this dosage form at a price equivalent to $0.77 per gram, while American Pharmaceutical offered it at $0.43, Evron at $0.45, Raway at $0.27, and Veltex at $0.35.

Unlike the marketing situation relating to procaine penicillin and potassium penicillin, which are offered by many sellers at widely varying prices, benzathine penicillin is sold by a limited number of companies at a uniform price. Only those companies may sell this product which were authorized to do so as a result of the benzathine penicillin interference settlement agreements.

On February 3, 1953, a basic product patent (U. S. Patent 2,627,-491) covering benzathine penicillin was issued to Wyeth. Prior to this date Wyeth's patent application had been in several interferences with applications of Pfizer, Lilly, and Bristol. In connection with the settlement of these interferences, early in 1953 Wyeth granted Pfizer, Lilly, and Bristol nonexclusive licenses to make, use, and sell benzathine penicillin. This product is said to remain active in the blood stream for a period longer than any other known forms of penicillin, including procaine penicillin. The total quantities of benzathine penicillin sold during the years covered by this report were relatively small, and the prices charged to the retailer by the sellers have been maintained at a level considerably higher than that of procaine penicillin.

Pfizer's trademark for benzathine penicillin is Permapen, while Wyeth's is Bicillin.[15] A representative dosage form comprising 10 disposable cartridges with sterile needle, each cartridge containing 600,000 units of benzathine penicillin, has been selected to illustrate the prices at which Pfizer and Wyeth sell their respective brands of benzathine penicillin. Commencing with 1954, both companies charged an identical price of $11.30 to the retailer for this dosage form. No suggested price to the consumer was reported by Wyeth. Pfizer's suggested price to the consumer, as reported to the Federal Trade Commission, was $18.33. This price, like the price to the retailer, has remained unchanged since the product was introduced.

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[15] Lilly offers only one dosage form of benzathine penicillin (Neolin). Bristol offers only 2 dosage forms (Panbiotic) both of which contain combinations of benzathine penicillin with 2 other salts of penicillin.

Another benzathine penicillin dosage form marketed by Pfizer and Wyeth under their respective trademarks is what Pfizer calls Permapen Fortified. This dosage form is a mixture of procaine penicillin and benzathine penicillin and is sold in lots of 10 vials, each vial containing 300,000 units of benzathine penicillin and 300,000 units of procaine penicillin. The price to the retailer is $9 for 10 vials. Again, as in the case of the dosage form containing 600,000 units, this price has remained unchanged.

From the standpoint of pricing on the basis of potency, this combination dosage form presents the following aspects: The 10-vial package contains 3 million units of benzathine penicillin and 3 million units of procaine penicillin, or a total of 6 million units. Benzathine penicillin sold by itself has been priced to the retailer at $11.30 for 6 million units in 10-vial lots of 600,000 units each. If this price were used for comparison, the relative value of half that potency sold in combination dosage would be approximately $5.65 (one-half of $11.30). Ten-vial packages containing 3 million units of procaine penicillin were sold to retailers at $1.04 in 1954 (see table 43). On the basis of these individual substance prices, the price for 3 million units of each of the two when sold in combination would be on the order of $5.65 plus $1.04, or $6.69 for 10 vials instead of $9, the price which has been quoted since 1954, notwithstanding the fact that the price of 3 million units of procaine penicillin was reduced to $0.56 between 1954 and 1956.

There was similarity among the prices per gram of the broad spectrum antibiotics in 1956, considered more fully in a later section of this chapter, and erythromycin, phenoxymethyl penicillin, and benzathine penicillin. As shown in table 46, all of these antibiotics have been sold in tablets [16] in varying potencies ranging from 50- to 300-milligram antibiotic content per tablet, except benzathine penicillin tablets, the antibiotic content of which is measured in units. As to the latter, the price per gram of benzathine penicillin tablets has been computed on the basis of the theoretical potency of 1,211,000 units equaling 1 gram.[17]

Converted to the per-gram basis, the prices of these antibiotics in 1956 ranged from $1.51 per gram down to $1.12 per gram. For example, per-gram prices of broad spectrum antibiotics sold in tablet form varied from $1.51, for a bottle of 25 tablets, each of which contained 50 milligrams, down to $1.22, for 100 tablets, each of which contained 250 milligrams. These varying prices per gram appear to be related to at least two factors: (1) the potency of the particular

[16] The prices of those of the above-mentioned antibiotics which are sold in capsule form do not differ from the tablet form prices.

[17] Donald C. Grove and William A. Randall, Assay Methods of Antibiotics, a Laboratory Manual, Medical Encyclopedia, Inc., New York, N. Y., 1955, p. 19.

tablet, and (2) the number of such tablets in each package. As the potency per tablet increases, and as the number of tablets per package increases, the price per gram correspondingly decreases. (See table 46.)

Table 46 shows that prices per gram of broad spectrums, erythromycin, and penicillin V (phenoxymethyl penicillin) are at about the same level. For example, 100-milligram tablets of broad spectrums and erythromycin sell for between $1.44 and $1.38 per gram, depending upon the number of tablets per package. Penicillin V, in 125-milligram tablets, sells for $1.44 per gram.

A like similarity exists with respect to tablets of greater potency. Tablets containing 250 milligrams of broad spectrums or erythromycin sell for prices ranging between $1.28 and $1.22, depending upon the numbers of such tablets. Penicillin V sells for $1.20 per gram in both 250-milligram and 300-milligram tablet potencies, as indicated by table 46.

Benzathine penicillin is priced on a somewhat lower level than the aforementioned three groups of products. Only one company, Wyeth, sells benzathine penicillin in tablet form, and this company charges $1.21 per gram for 100 tablets, each containing 100,000 units, and $1.12 per gram for 36 tablets, each containing 200,000 units.

TABLE 46.—*Computed price per gram, broad spectrum antibiotics, erythromycin and penicillin specialties: 1956*

[In tablets and capsules]

Tablets	Pfizer	Lilly		Abbott	Wyeth	
	Broad spectrum	Erythromycin	Penicillin V	Erythromycin	Benzathine	Penicillin V
50 milligrams:						
25's (1.25 grams)	$1.51					
100's (5 grams)	1.45					
100 milligrams:						
25's (2.5 grams)	1.44			$1.44		
36's (3.6 grams)		$1.44				
100's (10 grams)	1.38	1.38		1.38		
125 milligrams:						
36's (4.5 grams)						$1.44
50's (6.25 grams)			$1.44			
250 milligrams:						
16's (4 grams)	1.28					
24's (6 grams)		1.27	1.20			
25's (6.25 grams)				1.27		
100's (25 grams)	1.22	1.22		1.22		
300 milligrams: 12's (3.6 grams)						1.20
100,000 units: 100's (8.25 grams)					$1.21	
200,000 units: 36's (5.95 grams)					1.12	

Source: FTC data request, 1957.

The foregoing comparisons indicate that broad spectrums, erythromycin, penicillin V, and benzathine penicillin were all sold to retailers in 1956 at a price in excess of $1 per gram, while the common

salts of penicillin, such as procaine penicillin and potassium penicillin, were sold at less than $1 per gram, and indeed, injection forms of these penicillin salts were priced to retailers as low as $0.15 per gram by some companies and as high as $0.45 per gram by other sellers. Tablet forms of these older penicillin salts sold at prices ranging from $0.14 to $0.91 per gram. As will be described more fully in the next subsection of this chapter, streptomycin and dihydrostreptomycin are sold by various sellers at prices between $0.22 per gram and $0.38 per gram.

Price history of selected streptomycin products

Bulk prices of streptomycin and dihydrostreptomycin.—There is a distinct similarity between the behavior of the bulk prices of streptomycin and dihydrostreptomycin, on the one hand, and the bulk penicillin prices, on the other hand. Both groups of bulk prices declined by more than 99 percent between the end of World War II, when they were made available for civilian use, and 1956.

Since the introduction of dihydrostreptomycin there has been no significant difference between the bulk prices of streptomycin and dihydrostreptomycin. Accordingly, the prices specified in table 47 below apply to both products. The prices of two representative companies, Pfizer and Merck, are presented for the purpose of illustrating the bulk price trends of the two products from their introduction through 1956. Prices of unlabeled dosage forms are included in this discussion of bulk streptomycin and dihydrostreptomycin.

In 1946, the bulk price was $16 per gram. By December 1948, this price had fallen to $0.819, a decrease of more than 95 percent. Between 1949 and 1952, bulk prices continued to fall, reaching a level of $0.1998 per gram in December 1952. Between 1953 and the first half of 1956, the price of one manufacturer (Pfizer) dropped to 7 cents on sales of 250 kilograms or more, while Merck quoted the same price for purchases of less than 500 kilograms, and a price of $0.06 for quantities over 1,000 kilograms on contract. During the second half of 1956, Pfizer's price increased to about 7.7 cents, and Merck increased its price to 7.6 cents. Thus, the total decrease between 1946 and 1955 amounted to about 99½ percent, which is approximately the same reduction as occurred in the sale of bulk penicillin during a comparable period.

As in the case of penicillin bulk, some of the manufacturers supplied bulk streptomycin and bulk dihydrostreptomycin under special contractual arrangements. As shown by table 47, these contract prices were on occasion considerably lower than the noncontractual bulk prices. In 1956, for example, the noncontractual bulk price was about 7 cents per gram, while the lowest contract price was 4.1 cents.

TABLE 47.—*Bulk* [1] *prices per gram, streptomycin and dihydrostreptomycin: 1946–56*

[In dollars]

Month	Year	Pfizer [2]	Merck [2]
February	1946	16.00*	
June	1946	12.50*	
October	1946	5.75	4.50.*
November	1946	4.50*	2.88.*
February	1947	2.80	
October	1947	2.00	2.18.*
December	1947	1.79*	1.79.*
		1.70	1.776.
March	1948	1.408*	
		1.33	
April	1948		1.408.*
			1.30.
May	1948	1.408*	
		1.30	
July	1948	1.024*	1.024.*
		0.92	0.92.
November	1948		Dihydrostreptomycin offerred at same price as streptomycin.
December	1948	0.8192*, 0.72 (dihydrostreptomycin offered at same price as streptomycin).	
March	1949	0.50*	0.512.*
		0.412	0.412.
December	1949	0.315*	0.384.*
		0.315	0.384.
February	1950		0.30* (contracts).
			0.231 (contracts).
March	1952	0.30*	
		0.27	0.27.
May	1952	0.24*	0.27.*
		0.21	0.24.
October	1952		0.27* (1,000 1-gram vials).
			0.18.
November	1952	0.21*	
		0.18 (less than 100 kilograms).	
		0.16 (100 kilograms or more).	
December	1952	0.1998*	0.27* (1,000 1-gram vials).
		0.18 (less than 100 kilograms)	0.16.
		0.16 (100 kilograms or more).	
February	1953	0.17	0.17.
October	1953	0.19*	0.24* (1,000 1-gram vials).
November	1953	0.19*	0.23* (1,000 1-gram vials).
March	1954		0.22* (1,000 1-gram vials).
			0.21* (2,000 1-gram vials).
			0.20* (5,000 1-gram vials).
			0.19* (10,000 1-gram vials).
			0.18* (25,000 1-gram vials).
			0.17* (50,000 1-gram vials).
			0.16* (100,000 1-gram vials).
December	1954	0.12996*	0.1325* (contracts).
		0.12	0.925 (contracts).
July	1955		0.125* (dihydrostreptomycin contracts).[3]
			0.127* (streptomycin contracts).[3]
			0.090.
September	1955		0.108* (dihydrostreptomycin contracts).[3]
			0.11* (streptomycin cotracts).[3]
			0.070 (contract less than 500 kilograms).
			0.065 (contract 500–1,000 kilograms).
			0.060 (contract over 1,000 kilograms).
April	1956	0.0745 (less than 50 kilograms)	
		0.0730 (50–99 kilograms)	
		0.0715 (100–249 kilograms)	
		0.0700 (250 kilograms or more)	
June	1956		0.041 (dihydrostreptomycin contract).[3]
			0.044 (streptomycin sulfate contract).[3]
July	1956		0.12* (dihydrostreptomycin contract).[3]
			0.11* (streptomycin contract).[3]
			0.0685 (less than 50 kilograms).
			0.0675 (50 kilograms or more).
October	1956	0.0775 (less than 50 kilograms)	
		0.0750 (50 kilograms or more)	
November	1956		0.0760 (less than 50 kilograms).
			0.0750 (50 kilograms or more).

[1] Prices of unlabeled dosage forms are included in this table, and are identified by an asterisk. Prices not accompanied by an asterisk are for bulk products sold as such.
[2] Both Merck and Pfizer reported certain bulk prices per kilogram, other bulk prices on a per gram basis. For preparation in this table, all kilogram prices were converted to per gram prices.
[3] Except as otherwise indicated, streptomycin and dihydrostreptomycin were identically priced.

Source: FTC data requests, 1956 and 1957.

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Dosage form prices for streptomycin and dihydrostreptomycin.—Just as in the case of the dosage form price movement of procaine penicillin, the dosage form prices of streptomycin and dihydrostreptomycin, taking 1 gram as a representative dose, were significantly reduced between 1948 and 1956. For purposes of illustration, prices of two sellers, Merck and Abbott, are presented in table 48. The greatest reduction in streptomycin dosage from prices, however, occurred prior to 1948, as was the case with sodium and potassium penicillin. Streptomycin was first sold in October 1945, at a price of $20 per gram. By November 1946, however, the price had declined to $4.80 per gram. It was not until December 1946 that streptomycin was released for general sale. Thereafter the price declined to $4 per gram in April 1947, and by March 1948, 1 gram was selling at a price of $2.20.

When dihydrostreptomycin was first introduced in November 1948, the going price for streptomycin was $1.60. Dihydrostreptomycin was quoted at the same price. Thereafter, prices of both of these products declined by identical amounts. One month later, in December 1948, the per gram prices of both products were further reduced to $1.28. By March 1949, prices had been lowered to $0.80 per gram, and in December 1949, the two products were selling at $0.60 per gram.

No change occurred in list prices of these products after this date until March 1952, when prices were lowered to $0.40 per gram. Reductions in list prices since that date have been relatively small, amounting to only a few cents. Both products were priced by Abbott at $0.33 per gram to retailers in 1955 and 1956, while Merck's catalog

TABLE 48.—*Prices of streptomycin and dihydrostreptomycin per 1-gram dosage form to retailers and hospitals from date of introduction through 1956*

	Merck		Abbott	
	Streptomycin	Dihydrostreptomycin	Streptomycin	Dihydrostreptomycin
October 1945	$20.00			
September 1946	16.00			
October 1946	8.00			
November 1946	4.80			
December 1946	4.80		$4.80	
April 1947	4.00		4.00	
August 1947	3.40		3.40	
December 1947	2.80		2.52	
March 1948	2.20		2.20	
July 1948	1.60		1.60	
November 1948	1.60	$1.60	1.60	
December 1948	1.28	1.28	1.28	$1.28
March 1949	.80	.80	.80	.80
December 1949	.60	.60	.60	.60
March 1952	.40	.40	.40	.40
January 1953	.36	.36	.36	.36
October 1953	[1] .32	[1] .32		
May 1955	.36	.36	.33	.33
January 1956	.36	.36	.33	.33

[1] 100-vial lots.

Source: FTC data requests, 1956–57.

price per single vial continued to be quoted at $0.36 even though Merck reported a price of $0.32 in October 1953 for 100-vial lots.

There has been much more intensive price competition in the sale of both streptomycin and dihydrostreptomycin than appears from published prices of these products. In addition to making periodic offers of "free goods," one company advised its district sales managers in 1954 as follows: [18]

As you know, we have been experiencing severe pressure from some of our competitors in the form of extra discounts and prices in the antibiotic product field. As a result of these prices, we have lost orders and are in danger of losing customers.

We feel that our listed prices are reasonable and fair, and intend to maintain them. On the other hand, we cannot afford to ignore any longer the prices which certain other manufacturers are giving in certain cases. Therefore, we are attaching, herewith, the lowest price which you can quote to meet this competition * * *

Dihydrostreptomycin sulfate crystalline 1-gm. solution	$0.20
Dihydrostreptomycin crystalline, 1 gm	.19
Streptomycin, 1 gm. (dry)	.20
Streptomycin sulfate, 1 gm. (dry)	.20

In August 1955, district sales managers of this manufacturer were empowered to sell these products for as low as $0.15 and $0.16 per gram in order to meet competition. Published prices of this manufacturer remained unchanged and at a higher level during this period. Information regarding competitive deviations from published prices is limited, hence no attempt has been made in this discussion to describe in detail the various prices actually charged by particular manufacturers to meet competition at specific times. Rather, the purpose has been merely to indicate the downward course of streptomycin and dihydrostreptomycin prices between 1946 and 1956.

Comparative prices quoted by various sellers of streptomycin and dihydrostreptomycin, 1956.—In the preceding section of this chapter, price trends of streptomycin and dihydrostreptomycin products since their introduction in 1945 and 1948, respectively, through 1956 have been recounted. There were 12 or more sellers of these products in every year after 1948, some of which manufactured streptomycin and/or dihydrostreptomycin themselves, others of which purchased the antibiotics in bulk, preparing dosage forms therefrom, and selling such dosage forms under their own labels.[19] In table 49, below, prices per gram to retailers by eight sellers of streptomycin and dihydrostreptomycin are compared. The most popular dosage forms appear to be either dry powder or solution of streptomycin

[18] Source: FTC data requests, 1956–57.

[19] It is not uncommon for companies to purchase already packaged, but unlabeled, dosage forms. These dosage forms are then resold to retailers, wholesalers, physicians, or hospitals under the reseller's own label.

or dihydrostreptomycin in 1-gram vials or in 5-gram vials. As indicated by table 49, the price per gram of each product is somewhat lower when sold in 5-gram vials than is the case when sold in 1-gram vials.

TABLE 49.—*Price per gram, streptomycin or dihydrostreptomycin sulfate, to retailers: 1956*

[In 1-gram and 5-gram vials]

Product and dosage form	Abbott	Lannett	Merck Sharp & Dohme	Parke, Davis	Pfizer	Upjohn	Veltex	Vitamix
STREPTOMYCIN								
Powder:								
1 gram	$0.33	$0.36	$0.36	$0.36	$0.33	$0.33	$0.29	---------
5 grams	---------	.24	.32	.32	.24	[1] .24	.22	---------
Solution:								
1 gram	---------	---------	.38	.38	.35	.35	.29	---------
5 grams	---------	---------	.34	.34	.26	.26	.22	---------
DIHYDROSTREPTOMYCIN								
Powder:								
1 gram	.33	.34	.36	.36	.33	.33	.29	$0.45
5 grams	.25	.22	.32	.32	.24	.24	.22	.35
Solution:								
1 gram	.35	---------	.38	.38	.35	.35	.29	---------
5 grams	---------	---------	.34	.34	.26	.26	.22	---------

[1] 10-gram size.

Source: Drug Topics Red Book, 1957 (published in the fall of 1956); FTC data request, 1957.

There is very little uniformity in prices per gram among the sellers of either product in any of the various dosage forms. For example, a 1-gram vial of streptomycin powder is priced to retailers at $0.29 by 1 seller, at $0.33 by 3 sellers, and at $0.36 by an additional 3 sellers. An even wider differential exists among prices per gram for streptomycin solution when sold in 5-gram vials, varying from $0.22 by 1 seller, to $0.26 by an additional 2 sellers, to $0.34 for 2 other companies.

Still wider disparities exist with respect to dihydrostreptomycin powder when sold in 1-gram vials. One distributor, Veltex, charges $0.29 per gram, 3 sellers charge $0.33, a fifth company charges $0.34, 2 other companies charge $0.36, and Vitamix Co. charges $0.45 per gram. A 5-gram vial of dihydrostreptomycin powder, as evidenced by table 49, is offered by the different companies at 5 different prices per gram, ranging from $0.22 to $0.35.

Each seller named in table 49 offering both streptomycin and dihydrostreptomycin, with the exception of Lannett, sells comparable dosage forms of the two products at the same price per gram. As an illustration, Merck, Sharp & Dohme offers 1 gram of streptomycin powder and 1 gram of dihydrostreptomycin powder each at $0.36 per gram. Five-gram vials of streptomycin solution or 5-gram vials of dihydrostreptomycin solution may be purchased from this company at a price of $0.34 per gram.

Government procurement of penicillin and streptomycin

Large quantities of dosage forms of penicillins and streptomycins are purchased by Federal Government agencies. Manufacturers quote lower prices to such agencies on large volume orders for centralized delivery than are quoted to wholesalers, retailers, and hospitals. For example, procurement for the Armed Forces is channeled through the Military Medical Supply Agency, which is the successor to the Armed Services Medical Procurement Agency. Other agencies which purchase large quantities of penicillins and streptomycins are the Veterans' Administration, the Department of Health, Education, and Welfare, and the Federal Supply Service of the General Services Administration.

A study of the prices paid by the Armed Services Medical Procurement Agency for penicillins and streptomycins on contract awards during the years 1949 through 1956 indicates that there was keen price competition among manufacturers, as a result of which the Government benefited. Two antibiotic dosage forms, both of which are bought in large volumes, have been selected to illustrate the prices paid by Government agencies during the years 1949 to 1956, inclusive. The first of these is procaine penicillin G for aqueous injection, purchased on the basis of 1,500,000 units per bottle, and the second is dihydrostreptomycin sulfate, in 1-gram quantity in bottles. Since these two representative dosage forms of penicillin and dihydrostreptomycin are sold in different amounts, their price histories will be discussed separately. It may be stated at the outset, however, that the patterns of price movements of the two substances are similar.

Procaine penicillin G.—Table 50 below lists the prices paid by the Armed Services Medical Procurement Agency for procaine penicillin G for large quantities stated in number of bottles of solution of the specified unit strength. The period covered is from July 1949 to October 1956.

On July 20, 1949, Squibb sold procaine penicillin G (1,500,000 units) to the Armed Services Medical Procurement Agency at a price of $1.09 per bottle. In August 1950, 13 months later, the same company offered the same product to the Armed Services Medical Procurement Agency for only $0.49 per bottle, a decline in price of more than 50 percent in little more than 1 year. To be sure, the quantity purchased from Squibb in 1950 was twice as great (64,200 bottles) as that purchased from Squibb in 1949 (30,000 bottles). The fall in price cannot be accounted for solely by the larger quantity purchased, however, since Lilly, at about the same time, sold 10,000 bottles to the same agency at $0.59 per bottle.

Thereafter, during the remainder of 1950 and through 1951, the price continued to fall gradually, to a level of $0.334 per bottle (on a purchase of 33,000 bottles) in February 1952.

TABLE 50.—*Prices paid by Armed Services Medical Procurement Agency for procaine penicillin G bottles of 1,500,000 units for aqueous injection: 1949–56*

[Number of bottles and price per bottle]

Contract date		Abbott Laboratories		Bristol Laboratories		Eli Lilly & Co.		Chas. Pfizer & Co.		E. R. Squibb & Sons	
Month	Year	Number	Price	Number	Price	Number	Price	Number	Price	Number	Price
July 20	1949									30,000	$1.09
Jan. 11	1950	280,000	$0.83								
June 22	1950	96,375	.59								
Aug. 31	1950									30,000	.49
										34,200	.49
Oct. 12	1950					10,000	$0.59				
Oct. 26	1950	18,000	.57								
		42,600	.57								
Jan. 29	1951					129,156	.42				
Apr. 3	1951					37,380	.44				
Apr. 27	1951									15,000	.49
June 7	1951					9,000	.43				
June 21	1951					64,000	.44				
June 25	1951									63,500	.47
Oct. 26	1951	46,500	.415							63,000	.47
		117,900	.42								
				62,000	$0.402						
				275,700	.402						
				46,500	.402						
Nov. 9	1951			[1] 24,000	.402						
Dec. 12	1951			[1] 237,600	.385						
Feb. 12	1952					[2] 33,000	.334				
June 10	1952							6,000	$0.245		
June 12	1952							217,800	.245		
Sept. 10	1952							15,000	.22		
								162,000	.22		
Apr. 6	1953			60,000	.20						
				261,000	.20						
Apr. 17	1953							132,000	.19		
June 8	1953			300,000	.179						
June 30	1953							48,000	.175		
Sept. 14	1953					60,000	.17				
Sept. 29	1953							80,400	.16		
Dec. 3	1953							24,000	.145		
Feb. 17	1954							48,000	.145		
June–October	1954										
								[3] 847,200	.142		
Apr. 7	1955					78,000	.115				
						[1] 265,800	.1123				

Apr. 15	1955							58,200	.102		
								42,000	.102		
Aug. 26	1955									31,800	.095
										84,000	.095
Jan. 20	1956							90,000	.11		
Mar. 6	1956									190,200	.105
										68,400	.105
										36,000	.105
May 23	1956									[1] 498,000	.109
										[1] 69,000	.109
										[1] 406,800	.109
Oct. 30	1956							36,000	.105		

[1] The price quoted was that charged at the point of origin of the goods sold.
[2] The price quoted has been averaged since part of the shipment was sent overseas at $0.35 per bottle and part was allocated to domestic needs at $0.35 per bottle.
[3] Total for 8 shipments.

NOTE.—Theoretical potency 1,009 units/mg. Grove & Randall, Assay Methods of Antibiotics, p. 18.

Source: Files of the Armed Services Medical Procurement Agency. A few purchases were made from companies other than those specified in this table.

The next sharp price reduction occurred in June 1952, when Pfizer sold 223,800 bottles at a price of $0.245 per bottle, a price almost 28 percent below that charged by Lilly only 4 months earlier. Bristol countered with a sale of 321,000 bottles at $0.20 per bottle on April 6, 1953. Thereupon Pfizer reduced its price to $0.19 for 132,000 bottles on April 17, 1953. Bristol cut its price to $0.179 per bottle on June 8, 1953, on a sale of 300,000 bottles. Pfizer responded on June 30, 1953, with a price of $0.175 on a quantity of 48,000 bottles.

On September 14, 1953, Lilly sold 60,000 bottles at $0.17 per bottle, and 2 weeks later Pfizer sold 80,400 bottles at $0.16 per bottle. By December 1953, Pfizer was selling for $0.145 per bottle. This price was not met by any competitors during the remainder of 1953. In June 1954, Pfizer sold an additional 48,000 bottles at the same price ($0.145 per bottle). During the succeeding 6 months, Pfizer delivered 847,200 bottles, divided among eight shipments, at 0.142 per bottle.

On April 7, 1955, Lilly sold 330,000 bottles at a price averaging about $0.113, almost 3 cents per bottle below Pfizer's price in 1954. Eight days later, on April 15, Pfizer's price was reduced to $0.102 per bottle on a sale of 100,200 bottles.

E. R. Squibb's first sale of procaine penicillin G (1,500,000 units) to the Armed Services Medical Procurement Agency since mid-1949 occurred on August 26, 1955. Almost 116,000 bottles were sold at a price of $0.095 per bottle, more than one-half cent per bottle lower than Pfizer's price in April 1955. Pfizer sold 90,000 bottles to the Armed Forces at a price of $0.11 per bottle on January 20, 1956. This was the first increase in prices of procaine penicillin G (1,500,000 units for aqueous injection) since 1951.

On March 8, 1956, 294,600 bottles were purchased from Squibb at a price of $0.105 per bottle. An additional 973,800 bottles were supplied by Squibb at a price of $0.109 per bottle on May 23, 1956.

The last purchase reported by the Armed Services Medical Procurement Agency (for the period covered in this report) occurred on October 30, 1956. Pfizer supplied 36,000 bottles at a price of $0.105 per bottle.

During the years 1949–56 the price fell from $1.09 per bottle to $0.105 per bottle, a decline to a level of less than one-tenth of the 1949 price. It should be observed that the quantity sold in 1949 for $1.09, 30,000 bottles, was almost the same as the quantity of 36,000 bottles sold in October 1956 for a price of $0.105 per bottle.

Dihydrostreptomycin sulfate.—Turning now to the history of contract prices paid by the Government for streptomycins, table 51 presents the quantities specified in bottles of dihydrostreptomycin sulfate purchased by the Armed Services Medical Procurement Agency during the period from October 1949 to October 1956. The prices of

TABLE 51.—*Prices paid by Armed Services Medical Procurement Agency for dihydrostreptomycin sulfate, 1 gram: 1949–56*

[Number of bottles[1] and price per bottle]

Contract date		Heyden Chemical Corp.		Eli Lilly & Co.		Merck & Co., Inc.		Chas. Pfizer & Co.	
Month	Year	Number	Price	Number	Price	Number	Price	Number	Price
Oct. 13	1949	51,000	$0.51						
Jan. 5	1950	12,000	.384						
Mar. 20	1950					18,000	$0.315		
Aug. 10	1950							30,000	$0.27
Aug. 30	1950							30,000	.29
Do	1950							43,200	.29
Oct. 30	1950							48,000	.30
								20,400	.30
Dec. 5	1950							60,000	.32
								74,400	.32
Mar. 1	1951							33,000	.33
Mar. 15	1951							120,000	.32
June 21	1951							29,000	.30
Sept. 21	1951							42,000	.34
Oct. 21	1951							37,500 26,400	.34
Jan. 5	1952							575,000	.34
Jan. 25	1952							22,800	.325
								24,000	.325
Apr. 11	1952							273,700	.23
Oct. 6	1952	60,000	.15						
Jan. 9	1953	90,000	.15						
Apr. 5	1953			108,000	$0.1389				
				48,000	.1389				
June 8	1953					30,600	.1421		
June 15	1953					96,000	.1568		
Sept. 29	1953			32,400	.15				
May 4	1954					80,400	.123		
June 11	1954					13,400 50,000 42,000 30,000 24,600	.123 .123 .123 .123 .123		
Oct. 12	1954					25,800	.123		
Dec. 16	1954					102,000	.123		
Apr. 15	1955							300,000	.079
May 23	1955							31,200	.079
Jan. 4	1956							37,200	.071
Jan. 25	1956					200,000	.079		
June 13	1956							66,666 33,334	.1175 .1175
Oct. 30	1956							27,000 24,000	.10 .10

[1] A bottle contains 1 gram.

Source: Files of the Armed Services Medical Procurement Agency. A few purchases were made from companies other than those specified in this table.

dihydrostreptomycin sulfate (1 gram) to the Armed Services Medical Procurement Agency have followed a pattern similar to the prices of procaine penicillin G (1,500,000 units), discussed above.

On October 13, 1949, Heyden Chemical Corp. sold 51,000 bottles of dihydrostreptomycin sulfate, each bottle containing 1 gram of that antibiotic, at a price of $0.51 per bottle. On January 5, 1950, Heyden reduced its price to $0.384 per bottle, selling 12,000 bottles at this price.

Two and one-half months later, Merck's price on 18,000 bottles of this product was $0.315, a reduction of 7 cents per bottle.

Pfizer entered the field in August 1950, lowering the price to $0.27 per bottle on a sale of 30,000 bottles. During the remainder of 1950, all throughout 1951, and until October of 1952, the purchases of dihydrostreptomycin sulfate by the Armed Services Medical Procurement Agency from Pfizer totaled 1,039,400 bottles. Table 51 shows that the price per bottle during this period varied from a high of $0.34 per bottle in September 1951 to a low of $0.23 in April 1952.

In October 1952, Heyden sold 60,000 bottles at a price of $0.15 per bottle, and 90,000 bottles at the same price in January 1953. During the remainder of 1953, Eli Lilly furnished 156,000 bottles in April at $0.1389, and 32,400 bottles in September at a price of $0.15 per bottle. Merck supplied 30,600 bottles at $0.1421, and 96,000 bottles at $0.1568, both sales occurring in June 1953.

During 1954, Sharp & Dohme division of Merck & Co. supplied 368,200 bottles of dihydrostreptomycin sulfate at a price of $0.123 per bottle.

A price decline of over 35 percent occurred in April 1955. During this month Pfizer sold 300,000 bottles to the Armed Services Medical Procurement Agency at a price of $0.079 per bottle, almost $0.045 per bottle less than Merck's price 4 months earlier. Pfizer continued this price through 1955. Early in January 1956, Pfizer lowered the price again to $0.071 per bottle on 37,200 bottles. Two hundred thousand bottles were sold by Merck at $0.079 per bottle on January 25, 1956.

Thereafter, Pfizer's price rose to $0.1175 per bottle on a sale of 100,000 bottles on June 13, 1956, but by October 1956, Pfizer's price was down to $0.10 per bottle. This was the last Armed Services purchase of dihydrostreptomycin sulfate during the period covered by this report.

The price history of sales of dihydrostreptomycin sulfate to the Armed Services Medical Procurement Agency recorded in table 51 supports the following conclusions:

(1) Prices of dihydrostreptomycin sulfate to the Armed Services declined almost continuously during the years 1949–56. By early 1956, the price of 1 gram of dihydrostreptomycin was

about 14 percent of the 1949 level; by late 1956 prices had risen to about 20 percent of the 1949 level.

(2) The pattern of the major price reductions during this period, in which first one and then another of the principal manufacturers became the supplier at reduced prices, indicates keen competition among Heyden,[30] Lilly, Merck, and Pfizer in an effort to obtain contracts to sell dihydrostreptomycin sulfate to the Armed Services Medical Procurement Agency.

Relative movement of penicillin and streptomycin dosage form prices to the Government and to civilians.—As heretofore stated, penicillin and streptomycin dosage form prices to the Government on contracts to purchase large quantities have always been considerably lower than those to the civilian population. These price differences reflect in part the large quantities which are purchased by the Government, and in part the elimination of wholesale and retail markups.

Although manufacturers' prices to the Government have usually been lower than those to the retailers and hospitals for civilian use, the percentage decreases to both Government and retailers between 1948 and 1956 were quite similar. For example, manufacturers' prices for procaine penicillin G to the Armed Services shown in table 50, decreased between 1949 and 1956, inclusive, by about 90 percent, whereas the decrease in price to retailers as shown in table 43 was about 94 percent. Observance by retailers of the manufacturers' suggested resale list prices would mean a comparable reduction in price to the ultimate consumer.

For dihydrostreptomycin, the showing for the same period is as follows: Based on dosage form prices shown in table 48, the price per gram of this product to retailers and hospitals declined during the period from November 1948 (when dihydrostreptomycin was introduced) to 1956 by about 80 percent. During approximately the same period that these reductions to retailers and hospitals occurred, prices to the Armed Services Medical Procurement Agency, as shown in table 51, declined also by about 80 percent.

Price history of the broad spectrum antibiotics

The four antibiotics which comprise the broad spectrum group are Aureomycin, Chloromycetin, Terramycin, and tetracycline. Chronologically, Aureomycin and Chloromycetin were the first broad spectrums to reach the market. Aureomycin was introduced on December 1, 1948, the principal dosage form being the 250-milligram capsule. This has continued to be the most important dosage form, not only for Aureomycin but also for the remaining broad spectrum antibiotics. For purposes of convenience, prices for broad spectrum antibiotics will

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[30] Heyden's antibiotic division was acquired by Cyanamid in November 1953.

be discussed with reference to the standard bottle of 16 capsules, each capsule containing 250 milligrams of the particular antibiotic to which reference is made.

Aureomycin was introduced at a price to retailers and hospitals of $15 per 16 capsules on December 1, 1948.[21] On February 1, 1949, about 2 months before Parke, Davis & Co. reached the market with Chloromycetin, the second broad spectrum antibiotic, Cyanamid reduced its price for Aureomycin by one-third, from $15 to $10. On March 25, 1949, Parke, Davis & Co. commenced selling 250-milligram capsules of Chloromycetin at a price per capsule equal to the reduced price of Aureomycin. Thereafter the prices for these two products did not change for about 1 year.

On February 1, 1950, Cyanamid and Parke, Davis reduced prices by 20 percent on their respective broad spectrum specialties, from $10 to $8. Two months later, Pfizer's Terramycin, the third broad spectrum antibiotic, made its appearance at a price of $8.40; i. e., 5 percent above the prices of Aureomycin and Chloromycetin. Incidentally, this product inaugurated Pfizer's entry into the ethical drug market under its own label.

One month later, on May 1, 1950, Cyanamid and Parke, Davis reduced prices on Aureomycin and Chloromycetin by 25 percent, from $8 to $6. Pfizer reduced the price of Terramycin on November 1, 1950, from $8.40 to $6, thus matching the prices of Cyanamid and Parke, Davis for Aureomycin and Chloromycetin, respectively.

The next broad spectrum price reduction was initiated by Pfizer on September 27, 1951. On this date Pfizer lowered Terramycin prices 15 percent, from $6 to $5.10. Four days later, Cyanamid and Parke, Davis met this price by reducing Aureomycin and Chloromycetin prices from $6 to $5.10. There were no further changes in the published prices of broad spectrum antibiotics to the retail drug trade from October 1951 to the end of the period covered by this price study, the fall of 1956.

Between December 1948 and October 1951, there was a strong similarity between the downward course of dosage from prices of procaine penicillin, streptomycin, and dihydrostreptomycin, on the one hand, and the three then existing broad spectrum antibiotics on the other.

During the period in question, Aureomycin declined from its introductory price of $15 in December 1948 to $5.10 in October 1951, or to approximately 34 percent of its original level. Chloromycetin, introduced at $10 in 1949,[22] fell to $5.10 in October 1951, or 51 percent of

[21] Aureomycin was introduced under the name Duomycin; on December 27, 1948, the name was changed to Aureomycin.

[22] Parke, Davis introduced Chloromycetin at the same price per capsule as that of Aureomycin. However, Parke, Davis offered Chloromycetin bottles of 12 capsules at $7.50 while Aureomycin was offered in bottles of 16 capsules of $10. Since in this discussion the 16-capsule dosage form was taken as the standard, the introductory price of Parke, Davis to the retailer has been adjusted to that standard.

its opening price. Terramycin, first marketed in April 1950 at a price of $8.40, fell to $5.10 in October 1951, or about 61 percent of the introductory price.

During the years 1948–51 the price of procaine penicillin (3-million unit dose in aqueous suspension) fell from $10 to $3.25, or to about 33 percent of the 1948 price. Streptomycin and dihydrostreptomycin prices declined from $1.28 per gram in December 1948 to $0.40 per gram in March 1952, or to about 31 percent of the 1948 price. These prices were published prices during the period in question and do not indicate the extent to which lower procaine penicillin, streptomycin, dihydrostreptomycin, and broad spectrum prices may have been quoted by particular sellers at specific times during this period. For present purposes, however, published prices are sufficient, since these prices indicate the extent to which there was similarity in price *trends* among procaine penicillin, streptomycin, dihydrostreptomycin, and the broad spectrum antibiotics between 1948 and 1951. However, as heretofore pointed out, insofar as sales to the retail drug trade were concerned, the prices of the three broad spectrum antibiotics remained uniform and unchanged after October 1, 1951, while the dosage form prices of penicillin, streptomycin, and dihydrostreptomycin continued to decline after that date.

The fourth and most important broad spectrum antibiotic, tetracycline, which now leads the others in sales, was first offered to retailers by Cyanamid under the trademark Achromycin on November 16, 1953, at $5.10, the same price at which the other three broad spectrums were then selling. All four broad spectrums have continued to sell to retailers at this same price.

Subsequently four other companies reached the market with their own brands of tetracycline: Bristol-Myers & Co. on April 30, 1954; Olin Mathieson Chemical Corp. (E. R. Squibb & Sons) on September 16, 1954; Chas. Pfizer & Co., Inc., on October 1, 1954; and The Upjohn Co. on October 11, 1954. Each company's own brand was introduced at the price of $5.10, the price at which all other broad spectrums were selling.[23] The entrance of Bristol, Olin Mathieson, and Upjohn into the sale of tetracycline is accounted for by licensing arrangements relating to the tetracycline product patent. These arrangements are described in chapter VIII of this report.

The $5.10 amount represents the price quoted to the retailer for 16 capsules, each containing 250 milligrams, of either of the four broad spectrum antibiotics. The "list" or "regular" price to consumers has been $8.50.[24] In States where "fair trade" laws have been in effect,

[23] Olin Mathieson and Upjohn are not original manufacturers of tetracycline; they purchase the product in bulk (including unlabeled dosage forms) from Bristol and sell it under their own trademarks and under their own labels.

[24] American Druggist Blue Book, 1956–1957, published by The American Druggist, New York.

TABLE 52.—*Broad spectrum antibiotic prices (16 250-milligram capsules): 1948–56*

Date	Aureomycin		Chloromycetin		Terramycin		Tetracyclines									
							Achromycin		Polycycline		Steclin		Tetracyn		Panmycin	
	Retailer	Consumer	Retailer	Consumer	Retailer	Consumer	Retailer	Consumer	Retailer	Consumer	Retailer	Consumer	Retailer	Consumer	Retailer	Consumer
Dec. 1, 1948	$15.00	$25.00														
Feb. 1, 1949	10.00	16.67														
Mar. 25, 1949			[1] $10.00													
Jan. 25, 1950			10.00													
Feb. 1, 1950	8.00	13.34	8.00													
Apr. 1, 1950					$8.40											
May 1, 1950	6.00	10.00	6.00													
Nov. 1, 1950					6.00											
Sept. 27, 1951					5.10	$8.50										
Oct. 1, 1951	5.10	8.50	5.10	$8.50	5.10	8.50										
Nov. 16, 1953	5.10	8.50	5.10	8.50	5.10	8.50	$5.10	$8.50								
Apr. 30, 1954	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	$5.10	$8.50						
Sept. 16, 1954	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	$5.10	$8.50				
Oct. 1, 1954	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	$5.10	$8.50		
Oct. 11, 1954	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	$5.10	$8.50
Dec. 31, 1955	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50
Dec. 31, 1956	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50	5.10	8.50

[1] Parke, Davis introduced Chloromycetin in 1949 at the same price per capsule as Aureomycin. However, the company offered it at that time in bottles of 12 capsules at $7.50, while 16 capsules of aureomycin sold for $10. Since computations in this table are based on a 16-capsule standard, Parke, Davis' introductory price to the retailer has been adjusted to this standard.

Source: FTC data requests, 1956 and 1957.

the "fair trade" price for Aureomycin, Chloromycetin, and certain brands of tetracycline has been $7.65. The price of broad spectrums to wholesalers varied between 47.4 percent and 51 percent of the $8.50 "list" or "regular" price to the patient. Table 52 presents the record of broad spectrum antibiotics prices for a selected dosage form from the time the first such product, Aureomycin, was introduced on December 1, 1948, through and including 1956.

Government procurement of broad spectrum antibiotics

As in the case of penicillins and streptomycins and, of course, other prescription drugs, the Federal Government is also a large purchaser of broad spectrum antibiotics. Certain agencies, such as the Armed Services Medical Procurement Agency and the Veterans' Administration, have been selected as illustrative of the price pattern of broad spectrum antibiotics in sales to the Government.

Armed Services Medical Procurement Agency.—All prices shown in table 53 below are based on orders calling for bottles of 100 capsules or tablets, each tablet or capsule containing 250 milligrams of a particular broad spectrum antibiotic. The prices in the columns headed "ASMPA" are for purchases by the Armed Services Medical Procurement Agency made on the dates shown.

This table includes data as to broad spectrum prices to hospitals and retailers, and to consumers, in addition to price quotations by manufacturers of these products to the Armed Services Medical Procurement Agency. The reason for including retail, hospital, and consumer price quotations is not so much to compare these prices with those paid by the ASMPA, but rather to compare the prince *trends* of the same products to different classes of customers. Accurate price comparisons based upon data in table 53 are impossible for several reasons. First of all, the quantities purchased by ASMPA are quite large. Also, certain quantity discounts are allowed to retail and hospital customers of broad spectrum producers, and these discounts are not reflected in the published price quotations to retailers and hospitals listed in table 53. Then too, retail and hospital customers receive a different type service from manufacturers than does the Government. Consumers purchase from retailers or hospitals, and not from manufacturers, which is another reason why no comparisons may be made between price quotations to retailers, hospitals, and consumers, on the one hand, and to the ASMPA, on the other hand.

Table 53 has a limited and specific purpose, which is to show that broad spectrum antibiotics prices to the ASMPA declined prior to and *after* October 1, 1951, while published prices of the same products to retailers, hospitals, and consumers declined prior to October 1, 1951, but remained unchanged after that date.

TABLE 53.—*Broad spectrum prices to the Armed Services Medical Procurement Agency, the retailer and the consumer: July 1949–October 1956*

[In quantities of 100 capsules or tablets of 250 milligrams each]

Month	Year	American Cyanamid Co.—Aureomycin			Parke, Davis & Co.—Chloromycetin			Chas. Pfizer & Co., Inc.—Terramycin			American Cyanamid Co.—Achromycin (Tetracycline)		
		ASMPA	Hospital and retailer	Consumer	ASMPA	Hospital and retailer	Consumer	ASMPA	Hospital and retailer	Consumer	ASMPA	Hospital and retailer	Consumer
July	1949	$44.50			$52.00								
November	1949	33.00											
November	1949	19.79											
January	1950				41.60								
May	1950				31.25								
June	1950							$28.80					
July	1950				30.00	$36.00	$60.00						
September	1950		$36.00	$60.00				28.22					
October	1950				20.00								
January	1951	18.00						19.50	$36.00	$60.00			
February	1951				18.00								
April	1951							19.00					
October	1951	15.30	30.60	51.00	15.30	30.60	51.00	15.00	30.60	51.00			
March	1952	15.00	30.60	51.00									
June	1953				12.50	30.60	51.00						
January	1954							12.81	30.60	51.00			
April	1954							12.04	30.60	51.00			
May	1954	12.00	30.60	51.00									
March	1955							11.47	30.60	51.00			
April	1956	11.00	30.60	51.00	12.50	30.60	51.00	10.97	30.60	51.00			
October	1956										$11.00	$30.60	$51.00

Source for armed services prices: File of the Armed Services Medical Procurement Agency.
Source for retail, hospital, and consumer prices: FTC data requests, 1956 and 1957.

The table shows that during the years 1949 through 1956, there was a steady decrease in prices paid by the Armed Services Medical Procurement Agency [25] for broad spectrum antibiotics.

The price per bottle of American Cyanamid's Aureomycin to ASMPA fell from $44.50 in 1949 to $11 in 1956. Similarly, the price of Parke, Davis' Chloromycetin per bottle was reduced from $52.50 in 1949 to $12.50 in 1953. Pfizer's Terramycin was sold to the agency for the first time in June 1950 at $28.80. By 1956, this price had been reduced to $10.97. When the agency made its first purchase of Cyanamid's brand of tetracycline (Achromycin) in October 1956, the price was $11 per bottle.

Thus, the prices charged to the Agency declined prior to as well as after October 1, 1951, while there were no decreases of the published prices to retailers, hospitals, and consumers after October 1, 1951.

Veterans' Administration purchases of tetracycline.—The Veterans' Administration also buys tetracycline from various manufacturers in bottles of 100 capsules of 250 milligrams each.

The Veterans' Administration has paid higher prices than has the Armed Services Medical Procurement Agency. Of course, purchases made by the ASMPA have been for comparatively large quantities to be released to a central depot, whereas total quantities purchased by the Veterans' Administration have been smaller. However, Veterans' Administration purchases of tetracycline have been substantial and have amounted to about $1 million annually.

According to the records of the Veterans' Administration, Cyanamid's Achromycin was put on a decentralized purchase contract basis by this agency in May 1954 at a price of $24.22, less 2 percent discount. Pfizer's Tetracyn was put on decentralized purchase contract at the same price in August of 1954. This was the price at which both companies sold their respective brand of tetracycline to drug wholesalers during the period covered by this report. These prices are for 100 capsules of tetracycline hydrochloride, each capsule containing 250 milligrams of this antibiotic.

In October 1954, Cyanamid and Pfizer were asked by the Veterans' Administration to offer a price reduction on a quantity of tetracycline to be delivered to the three VA depots instead of to individual hospitals. Cyanamid offered a price 10 percent below its former price of $24.22, or $21.80, whereas Pfizer reduced its price to $19.58, less 2 percent discount.

[25] As of January 1957 the Armed Services Medical Procurement Agency was succeeded by the Military Medical Supply Agency.

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Thereafter Cyanamid sold Achromycin directly to the VA hospitals at Pfizer's price of $19.58, less 2 percent discount. The contracts which established the foregoing price reductions expired on March 31, 1955. Shortly before March 31, 1955, the Veterans' Administration for the first time solicited competitive bids for tetracycline. The request for bids called for centralized (depot) and decentralized (hospital) deliveries commencing after March 31, 1955. Between March 1955 and July 1956, the agency asked for bids on a total of seven contracts to supply tetracycline in quantities ranging from 3,000 to 29,952 bottles of 100 capsules, each containing 250 milligrams of this antibiotic. In every instance the bids submitted by the three manufacturers—Cyanamid, Pfizer, and Bristol—and by the two licensed distributors—Upjohn and Olin Mathieson—were practically identical with the exception of some difference as to the time allowed to claim the 2-percent discount for cash payment. On one occasion McKesson & Robbins also submitted a bid to deliver either Cyanamid's or Pfizer's tetracycline. However, the price of that company did not vary from the price of the others, $19.58 less 2 percent discount per bottle. On the two largest contracts, calling for 28,992 and 29,952 bottles, respectively, Pfizer bid $19.188 net, which is $0.0004 less than $19.58, minus 2 percent discount for cash payment. Thus Pfizer was the low bidder.

Tetracycline purchases by the VA and by the ASMPA in 1956.—On October 5, 1956, Armed Services Medical Procurement Agency made its first purchase of tetracycline. The contract, which called for approximately 90,000 bottles, each containing 100 tablets of 250 milligrams of this antibiotic, was awarded to Cyanamid as the low bidder at a price of $11 per bottle.[26]

Two weeks later, on October 19, 1956, the Veterans' Administration opened bids on contracts to deliver the following quantities of bottles containing 100 capsules of 250 milligrams of tetracycline to the indicated depots:

Depot:	Number of bottles
Somerville, N. J	10, 080
Do	10, 080
Wilmington, Calif	3, 840
Do	3, 840
Hines, Ill	11, 280
Do	11, 280
Total	50, 400

[26] This was the price at which Cyanamid sold several large quantities of Aureomycin capsules to the Armed Services Medical Procurement Agency beginning in April 1956.

The following bids were submitted:

Bidder	Payment discount	Price offered
Pfizer	2 percent—30 days	$17.63.
McKesson & Robbins	Net	$19.188 ($19.58 less 2 percent discount is $19.1884).
Squibb	2 percent—30 days	$19.58.
Bristol	do	$19.58.
Cyanamid	do	$19.58.
Upjohn	do	$19.58.

Pfizer's low bid of $17.63 for the above-stated quantities was far out of line with Cyanamid's contract price of $11 quoted to the Armed Services Medical Procurement Agency 2 weeks earlier. The other companies, except for McKesson & Robbins, bid the identical price of $19.58, less 2 percent, to the Veterans' Administration. McKesson & Robbins' bid was $0.0004 per bottle less. Thus, within a period of 2 weeks, Cyanamid offered to sell tablets and capsules, which are ordinarily identically priced, to two United States Government agencies at widely differing prices: $11 to the Armed Services Medical Procurement Agency (tablets), and $19.58 to the Veterans' Administration (capsules).

The Market Share of Each Broad Spectrum Antibiotic Relative to Total Broad Spectrum Sales, 1951-56

While published prices of the broad spectrum antibiotics to the drug trade remained uniform and unchanged, significant shifts in their relative market importance took place after October 1, 1951.

In 1951, measured by the total quantities of sales, the market for broad spectrums for medicinal uses was divided as follows among the three products then being produced and sold:

	Percent
Chlortetracycline (Aureomycin)	41. 5
Chloramphenicol (Chloromycetin)	36. 5
Oxytetracycline (Terramycin)	22. 0

Aureomycin's share of the market declined to 13.2 percent by 1955. Chloromycetin's market share declined to 9 percent in 1954 and increased to 12.6 percent in 1955.

In 1953, tetracycline made its commercial appearance, and acquired 2.8 percent of the broad spectrum market in its first year. By 1955, tetracycline's [27] share of total broad spectrum sales for medicinal

[27] Tetracycline is referred to by its generic name in the text of this chapter. Pfizer makes and sells it under the trade name Tetracyn. Its two other makers, Bristol and American Cyanamid, sell it, respectively, as Polycycline and Achromycin. Upjohn and Squibb, buyers in bulk from Bristol, sell in dosage forms under their respective trade names, Panmycin and Steclin.

purposes had increased to 43.6 percent, thus becoming the leading product among the broad spectrums.

This shift in favor of tetracycline actually strengthened the relative market positions of Cyanamid and Pfizer. By virtue of licensing arrangements relating to tetracycline between these two broad spectrum manufacturers, both companies benefited from the large increase of tetracycline sales. Indeed, the losses in sales of Cyanamid's Aureomycin and Pfizer's Terramycin were offset by the gains in sales of their respective brands of tetracycline. In addition, both Cyanamid and Pfizer receive royalties under the Aureomycin and tetracycline agreements, respectively. Furthermore, since tetracycline was introduced, significant amounts of Aureomycin and Terramycin have been sold for animal feed and agricultural purposes.

CHAPTER VII

Analysis of Financial Data Submitted by Antibiotics Manufacturers

Since 1941, when the pharmaceutical industry, encouraged and financially aided by the Government, commenced manufacture of penicillin, the antibiotics branch of the industry has grown rapidly. Approximately 20 companies have been active at various times in the manufacture of antibiotics, and, at present, 12 major manufacturers remain in the field. The "antibiotics industry" is a subdivision or part of the larger pharmaceutical industry, and in all cases the manufacture of antibiotics represents only a part of a firm's production. These characteristics, and the accompanying problems of determining or isolating accounting items, make the analysis of the financial organization and operations of the antibiotics branch of the industry difficult.

Size of Manufacturing Companies

The 1956 consolidated assets, net sales, sales of domestically produced antibiotics, and percent thereof to total sales of the firms engaged in the manufacture of antibiotics are shown in table 54.

TABLE 54.—*Consolidated net sales and assets and antibiotics net sales, by company: 1956*

[Assets and sales are shown in thousands of dollars]

Name of company	Consolidated				Antibiotics		
	Assets		Net sales		Net sales [1]		Percent of consolidated net sales
	Amount	Percent	Amount	Percent	Amount	Percent	
Total	2,395,324	100.0	2,434,899	100.0	337,718	100.0	[2] 13.9
Olin Mathieson	653,750	27.2	596,673	24.4	30,924	9.2	5.2
American Cyanamid	559,892	23.4	500,651	20.6	89,940	26.6	18.0
Lilly	195,646	8.2	181,530	7.5	31,918	9.5	17.6
American Home	169,484	7.1	295,483	12.1	21,986	6.5	7.4
Merck	168,017	7.0	172,432	7.1	[3] 16,424	4.9	9.5
Pfizer	152,583	6.4	178,362	7.3	70,334	20.8	39.4
Parke, Davis	139,262	5.8	134,093	5.5	24,637	7.3	18.4
Upjohn	107,851	4.5	111,013	4.6	22,598	6.7	20.4
Abbott	102,572	4.3	96,786	4.0	9,187	2.7	9.5
Commercial Solvents	74,580	3.1	58,745	2.4	3,504	1.0	6.0
Bristol-Myers	57,506	2.4	89,404	3.7	15,354	4.5	17.2
Penick	14,181	.6	19,727	.8	912	.3	4.6

[1] Sales of domestic production only.
[2] Industry average.
[3] Does not include sales of animal feed supplements and export sales.

Source: FTC data request, 1957, and published financial reports.

The companies have been ranked on the basis of their consolidated assets, but their relative positions as antibiotics manufacturers are quite different. Olin Mathieson, the largest company in both assets and sales, has only 5.2 percent of its sales in antibiotics, and it ranks no higher than fourth in antibiotics sales. Chas. Pfizer & Co., which ranks only sixth in assets, has the highest proportion of its total sales, namely, 39.4 percent, in domestically produced antibiotics and ranks second in antibiotics sales.

The two largest diversified companies, Olin Mathieson and American Cyanamid, have 50.6 percent of the consolidated assets of all 12 antibiotics manufacturers, and account for 45.0 percent of the total sales, including antibiotics and all other products. In antibiotics alone, their sales are 35.8 percent of the total, with Cyanamid accounting for about three-quarters of their combined share.

The fact that antibiotics constitute 39.4 percent or less of the total sales of each company is indicative of the fact that antibiotics manufacture constitutes a segment of the pharmaceutical industry rather than an independent industry. Excluding the five diversified companies (Olin Mathieson, American Cyanamid, American Home Products, Commercial Solvents, and Bristol-Myers), the balance of the industry has 19.7 percent of its total sales in antibiotics.

Company Sales of Antibiotics

Most of the companies which were requested to furnish the Commission accounting data covering the years 1950 through 1956 were manufacturers of one or more antibiotic substances during all or part of the above period. The balance had been manufacturers in prior years. It should be pointed out that antibiotics sales of individual reporting companies are not necessarily limited to items produced by their own manufacturing facilities. Purchases in bulk and other forms were frequently made for the purpose of supplementing production and for compounding and finishing types of antibiotics manufactured by other firms. In most instances the sale of antibiotic products in bulk and dosage forms represents a significant amount of the companies' aggregate dollar volume of sales, but such products may constitute a comparatively small part of the total number of their full line of pharmaceutical items.

In addition to the companies which are presently manufacturing antibiotics and those which were formerly in this field, there are nonmanufacturing pharmaceutical firms which may have substantial sales of antibiotic products. Such firms purchase the antibiotic substances in bulk and in semifinished form, for compounding and finishing into dosage form for resale under their own labels. Operations of these firms are not considered in this chapter.

Net sales of domestically produced antibiotics of the leading manufacturers for years 1956 and 1950 are shown in table 55. The companies have been ranked on the basis of their 1956 sales. The relative positions of four firms—American Cyanamid, Pfizer, Olin Mathieson, and Bristol-Myers—are unchanged with respect to the years shown.

Cutter, Monsanto, and Schenley, which were producers in 1950, discontinued the manufacture of antibiotics prior to 1956. In December 1953, Heyden Chemical Corp. (now Heyden Newport Chemical Corp.) sold all of the assets of its antibiotics division to American Cyanamid Co. Thus, 4 manufacturers with aggregate antibiotic net sales of $16,678,000 in 1950, representing 6.7 percent of total sales shown in the table for that year, are not included in the 1956 column. The $337,718,000 total sales in 1956 represent a 35.3-percent increase over the $249,623,000 total sales in 1950, and a 45.0-percent increase over the $232,945,000 sales of the same 12 companies in 1950.

This increase in sales between 1950 and 1956 was accompanied by a change in industry concentration. The $223,116,000 aggregate net sales of antibiotics of the 4 leading companies in 1956 represents 66.1 percent of the 12-company total. In 1950, 4 leading firms had aggregate antibiotics sales of $137,515,000, or 55.1 percent of the 16-company total for that year. Thus, there was an increase of 11.0 percentage points in the 4-company concentration ratio in this industry. Although American Cyanamid, Pfizer, and Olin Mathieson were first, second, and fourth in rank, respectively, in both years, Lilly, which ranked sixth in 1950, supplanted Parke, Davis in third position in the 1956 lineup.

TABLE 55.—*Sales of antibiotics, by company: 1956 and 1950*

[Sales of domestic production in thousands of dollars. Companies ranked according to 1956 sales volume]

Company name	1956		1950		
	Net sales	Percent of total	Net sales	Percent of total	Rank
Total	337,718	100.0	249,623	100.0	
American Cyanamid	89,940	26.6	57,555	23.1	1
Pfizer	70,334	20.8	31,535	12.6	2
Lilly	31,918	9.5	19,262	7.7	6
Olin Mathieson	30,924	9.2	22,481	9.0	4
Parke, Davis	24,637	7.3	25,944	10.4	3
Upjohn	22,598	6.7	10,404	4.2	10
American Home	21,986	6.5	12,804	5.1	8
Merck [1]	16,424	4.9	21,911	8.8	5
Bristol-Myers	15,354	4.5	12,600	5.0	9
Abbott	9,187	2.7	12,989	5.2	7
Commercial Solvents	3,504	1.0	5,316	2.1	13
Penick	912	.3	144	.1	16
Schenley			5,849	2.4	11
Heyden			5,833	2.3	12
Monsanto			3,520	1.4	14
Cutter			1,476	.6	15

[1] Does not include sales of animal feed supplements and in 1956, export sales.

Source: FTC data request, 1957.

The two companies which made the greatest dollar gains—and whose gains accounted for the entire percentage increase of the top four—Pfizer with a gain of $38,799,000 and American Cyanamid with one of $32,385,000, are the leading factors in the broad spectrum field, and sales of this group account for all or most of their sales gains. Two of the four companies next in rank, according to sales increase, Upjohn with a gain of $12,194,000 and Olin Mathieson with a gain of $8,443,000, were also in this field. Lilly and American Home Products, neither of which produced or sold a broad spectrum antibiotic, had gains of $12,656,000 and $9,182,000, respectively, due to the success of their recently discovered antibiotic specialties. Of the other six companies in the 1956 list, only Bristol-Myers, a broad spectrum producer, and Penick, whose volume was insignificant, showed any gain in sales.

Accounting Practices and Problems

By its second data request, a copy of which is included in this report as appendix 1, exhibit 2, the Commission in May of 1957 sought data from the companies regarding cost of production and profitability of manufacturing antibiotic products. The complete data sought by the Commission were not submitted by the manufacturers, and such data as were submitted have not been verified by the Commission. However, the corporations certified that their reports were true and made in good faith.

The reasons given for failure to submit certain categories of data included representations by the companies that the data sought were not available and could not be obtained without an inordinate amount of time and effort. It was pointed out by the companies that the substantial segment of personnel, space, production, and packaging facilities which may be used in the production of chemicals and other drugs as well as in antibiotics presented problems of allocation of costs; that few plants are used exclusively for the production of antibiotics; and that distribution of selling, general, and administrative expenses to the various antibiotics manufactured presented additional cost accounting problems.

Research, a significant item, was reported as an example of the type of expense which could not be accurately determined with respect to particular products. It was claimed by officials of the companies that constant research for, and discovery of, new antibiotic substances produced by the same organisms made the distribution of such expense to particular products meaningless. It was also claimed that although the accounting records of some manufacturers were designed to provide budgetary control, they did not reflect research expense relating to particular antibiotic products. It was stated that in some instances research programs are directed to diseases rather than to specific prod-

ucts, thus adding further complexities in connection with distribution of this expense.

It was apparent that no uniform system of accounts existed, and that costing practices among the manufacturers differed markedly. Several of the leading companies reported they were unable to extract the necessary information for distributing production costs to the various antibiotics manufactured, while others reported that they were able to furnish certain basic accounting data relating to costs of all antibiotics produced, treated as a class, but had no detailed records from which to determine individual antibiotic product costs, or costs of the various types of dosage forms.

Income and Expenses

Method of analysis

In making their reports to the Commission, the manufacturers made allocations of expenses between production of antibiotics and production of other items. They also made allocations of expenses among the various antibiotic products they manufactured. Certain companies applied methods of cost allocation which differed from those used by other reporting companies. The Commission has not verified the cost allocations made or methods used by the companies in determining their costs and profits. In general, the analysis in this chapter follows the classification of accounts as reported by the corporations. Certain adjustments were made,, however, in some instances in order to permit comparability of accounting data among companies.

The identity of individual companies with respect to financial data is not disclosed. Nor does this chapter attempt to report the manufacturer's cost or profit on specific products. Such information is generally regarded as confidential. The chapter does not attempt to show cost or profit on specific grades of antibiotics or on specific dosage forms. Thus, the cost and profit figures include antibiotics sold for nonmedical as well as those sold for medicinal purposes. It was the companies' representation that because of the multiplicity of items involved, such a breakdown of cost data was not available and could not be obtained without inordinate effort. Therefore, this chapter is restricted to showing by combined groups the ratios to net sales of the principal general classes of costs and expenses reported by the companies and the comparative annual changes in such ratios during the period from 1950 to 1956, inclusive. All ratios are expressed in percentages. They do not give any indication of actual dollar amounts of cost incurred or profit realized by any company.

With the foregoing explanation, the Commission hereinafter presents an analysis of the financial data reported by the manufacturers of antibiotics.

Individual producers

Selected financial ratios relating to the total antibiotics activities of each of the leading manufacturers during the years 1950 through 1956 are shown in table 56. In order to avoid disclosing the identity of individual companies, numbers have been used in place of company names. The companies have been ranked on the basis of their 1956 ratios of gross profit to net sales, which ranged from a high of 78.6 percent to a low of 22.4 percent. In 1950 the range was almost exactly the same. The 1956 ratio of net profit before taxes to sales ranged from a high of 40.5 percent to a low of 1.8 percent, and the 1950 ratio from 53.7 percent to a loss of 14.7 percent. Only Company No. 7 reported substantial income from royalties and licenses in 1956, 12.5 percent of net sales, although eight other companies reported up to 4.2 percent in this category.

Fifteen producers are represented in table 56 for 1950 through 1952. Thirteen firms are included in 1953, and 12 in each of the remaining 3 years. Certain detailed accounting data with respect to companies numbered 3, 7, 8, and 9 were either not furnished or were furnished on a noncomparable basis and were unusable for the purposes of this tabulation.

The following tabulation shows the range in the ratios of net profit and (loss) before Federal taxes to net sales, between 1950 and 1956, as reflected in table 56:

Company No.	Profit ratio	
	High	Low
1	53.7	37.9
2	32.2	4.1
3	33.8	9.1
4	30.9	8.2
5	30.3	(3.9)
6	24.4	9.4
10	14.8	(4.2)
11	8.4	0.9
12	13.0	(64.5)
13	32.0	(23.6)
14	8.0	(71.7)
15	17.2	(33.5)
16	43.4	(1.3)

The wide variations for individual companies and between companies stands out clearly from these figures. Three of the seven companies showing losses discontinued antibiotics operations; a fourth sold this part of its business; and the remaining three realized a profit in the most recent years. Company 1 remained in first place in all 7 years with respect to its rates of gross profit, net operating profit, and net profit before taxes.

TABLE 56.—*Selected financial ratios for antibiotics manufacturing, by company: 1950 to 1956*

[Items including income from royalties and licenses stated as a percent of net sales. Companies numbered in order of their 1956 gross profit ratios]

Item	1956											
	1	2	3	4	5	6	7	8	9	10	11	12
Net sales	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Cost of goods sold	21.4	26.8	26.9	34.5	38.4	39.2	48.8	53.4	55.0	61.1	64.2	77.6
Gross profit	78.6	73.2	73.1	65.5	61.6	60.8	51.2	46.6	45.0	38.9	35.8	22.4
Selling, general and administrative expenses:												
Selling	16.7	13.9	(1)	18.0	9.2	20.4	(1)	(1)	(1)	9.9	14.6	8.5
Advertising	9.7	10.1	(1)	10.1	5.2	10.3	(1)	(1)	(1)	5.5	---	1.1
Research	8.1	3.9	4.2	7.9	6.5	3.5	10.5	(1)	(1)	6.7	5.2	4.7
Administrative and general	7.7	14.2	(1)	14.2	6.2	8.0	(1)	(1)	(1)	14.1	2.1	6.8
Total	42.2	42.1	39.4	50.2	27.1	42.2	(1)	(1)	(1)	36.2	21.9	21.1
Net operating profit	36.4	31.1	33.7	15.3	34.5	18.6	(1)	(1)	(1)	2.7	13.9	1.3
Income from royalties and licenses	4.0	1.1	(1)	2 0	1.5	---	12.5	4.2	2.9	(2)	---	3.2
Net profit before Federal taxes	40.5	32.2	33.8	15.1	30.3	19.3	(1)	(1)	(1)	1.8	8.3	4.5
Export sales included in net sales	23.7	3.5	(1)	3.3	7.6	6.8	(1)	17.3	14.1	22.3	19.7	2.2
	1955											
	1	2	3	4	5	6	7	8	9	10	11	12
Net sales	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Cost of goods sold	24.8	25.9	30.9	36.0	56.8	41.8	50.0	51.2	50.5	66.7	68.5	107.9
Gross profit	75.2	74.1	69.1	64.0	43.2	58.2	50.0	48.8	49.5	33.3	31.5	(7.9)
Selling, general and administrative expenses:												
Selling	16.8	17.0	(1)	15.8	8.2	19.6	(1)	(1)	(1)	9.0	16.1	12.6
Advertising	8.0	9.2	(1)	16.1	4.3	13.9	(1)	(1)	(1)	5.8	---	1.7
Research	8.2	3.8	4.0	9.4	5.5	3.0	13.8	(1)	(1)	6.2	4.7	30.0
Administrative and general	7.5	17.7	(1)	14.1	5.3	7.7	(1)	(1)	(1)	12.3	3.4	11.4
Total	40.5	47.7	41.9	55.4	23.3	44.2	(1)	(1)	(1)	33.3	24.2	55.7
Net operating profit	34.7	26.4	27.2	8.6	19.9	14.0	(1)	(1)	(1)	---	7.3	(63.6)
Income from royalties and licenses	3.5	1.3	(1)	(2)	1.5	---	19.0	1.7	2.0	(2)	---	3.0
Net profit before Federal taxes	37.9	26.8	26.9	8.2	11.1	15.6	(1)	(1)	(1)	(2.8)	.9	(60.7)
Export sales included in net sales	22.1	4.5	(1)	2.4	9.3	8.6	(1)	22.8	15.4	27.2	19.8	10.4

See footnotes at end of table.

TABLE 56.—*Selected financial ratios for antibiotics manufacturing, by company: 1950 to 1956*—Continued

Item	1954											
	1	2	3	4	5	6	7	8	9	10	11	12
Net sales	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Cost of goods sold	22.7	29.3	46.3	39.0	53.0	43.3	48.5	49.2	69.0	70.4	65.0	111.0
Gross profit	77.3	70.7	53.7	61.0	47.0	56.7	51.5	50.8	31.0	29.6	35.0	(11.0)
Selling, general and administrative expenses:												
Selling	15.0	18.1	(1)	15.7	10.1	17.8	(1)	(1)	(1)	7.2	12.7	14.2
Advertising	9.8	8.9	(1)	10.4	6.1	18.9	(1)	(1)	(1)	4.4	—	3.0
Research	7.5	4.2	4.3	9.6	7.4	2.7	9.2	(1)	(1)	6.7	5.5	27.2
Administrative and general	7.4	19.2	(1)	13.6	7.1	8.9	(1)	(1)	(1)	11.4	3.1	4.5
Total	39.7	50.4	45.1	49.3	30.7	48.3	(1)	(1)	(1)	29.7	21.3	48.9
Net operating profit	37.6	20.3	8.6	11.7	16.3	8.4	(1)	(1)	(1)	(.1)	13.7	(59.9)
Income from royalties and licenses	2.5	.6	(1)	—	1.4	—	24.3	.3	2.6	.1	—	1.9
Net profit before Federal taxes	39.7	20.8	9.1	10.0	.4	9.4	(1)	(1)	(1)	(4.2)	8.4	(58.0)
Export sales included in net sales	26.8	4.7	(1)	3.0	13.2	9.9	(1)	24.2	24.5	41.2	—	11.0

Item	1953												
	1	2	3	4	5	6	7	8	9	10	12	13	14
Net sales	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Cost of goods sold	23.1	31.6	45.5	27.9	56.1	46.2	46.1	47.9	87.0	64.1	104.2	102.3	138.6
Gross profit	76.9	68.4	54.5	72.1	43.9	53.8	53.9	52.1	13.0	35.9	(4.2)	(2.3)	(38.6)
Selling, general and administrative expenses:													
Selling	14.5	15.4	(1)	14.8	9.8	15.3	(1)	(1)	(1)	8.1	6.8	3.2	9.1
Advertising	7.3	8.5	(1)	4.9	5.5	11.0	(1)	(1)	(1)	4.9	3.8	.5	2.8
Research	7.2	3.6	4.5	7.6	6.1	2.3	9.5	(1)	(1)	7.0	12.6	15.5	8.7
Administrative and general	7.0	18.3	(1)	13.8	8.4	8.6	(1)	(1)	(1)	12.1	4.3	4.0	11.9
Total	36.0	45.8	45.5	41.1	29.8	37.2	(1)	(1)	(1)	32.1	27.5	23.2	32.5
Net operating profit	40.9	22.6	9.0	31.0	14.1	16.6	(1)	(1)	(1)	3.8	(31.7)	(25.5)	(71.1)
Income from royalties and licenses	1.4	.2	(1)	—	1.2	—	28.5	.3	2.1	(2)	.6	1.9	—
Net profit before Federal taxes	42.0	21.2	9.6	30.9	10.1	17.5	(1)	(1)	(1)	(2)	(31.0)	(23.6)	(71.7)
Export sales included in net sales	29.7	3.8	(1)	1.7	11.4	13.8	(1)	21.3	36.1	32.7	11.0	54.2	20.5

Item	1952														
	1	2	3	4	5	6	7	8	9	10	12	13	14	15	16
Net sales	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Cost of goods sold	28.0	49.0	31.9	33.0	72.5	58.7	71.7	51.2	64.6	70.2	123.9	85.4	108.9	87.6	89.9
Gross profit	72.0	51.0	68.1	67.0	27.5	41.3	28.3	48.8	35.4	29.8	(23.9)	14.6	(8.9)	12.4	10.1
Selling, general and administrative expenses:															
Selling	13.6	16.2	([1])	13.7	10.0	14.2	([1])	([1])	([1])	8.5	11.2	2.2	11.3	17.5	5.0
Advertising	7.7	8.0	([1])	3.3	5.1	5.8	([1])	([1])	([1])	4.6	4.5	.5	4.2	7.8	
Research	7.4	3.6	3.6	6.7	5.7	2.3	13.0	([1])	([1])	6.4	20.9	18.8	11.3	6.3	1.8
Administrative and general	6.3	18.6	([1])	13.5	8.7	8.5	([1])	([1])	([1])	11.9	4.2	4.1	13.9	10.6	3.7
Total	35.0	46.4	38.0	37.2	29.5	30.8	([1])	([1])	([1])	31.4	40.8	25.6	40.7	42.2	10.5
Net operating profit	37.0	4.6	30.1	29.8	(2.0)	10.5	([1])	([1])	([1])	(1.6)	(64.7)	(11.0)	(49.6)	(29.8)	(.4)
Income from royalties and licenses	1.1	([2])	([1])	--------	.7	--------	20.0	.3	.7	1.7	([2])	1.9	--------	12.4	--------
Net profit before Federal taxes	37.9	4.1	31.1	29.7	(3.9)	10.8	([1])	([1])	([1])	(2.3)	(64.5)	(9.2)	(49.6)	(33.5)	(1.3)
Export sales included in net sales	22.3	3.4	([1])	5.5	19.9	20.2	54.2	17.7	32.4	34.1	13.4	61.2	23.9	52.1	--------
	1951														
	1	2	3	4	5	6	7	8	9	10	12	13	14	15	16
Net sales	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Cost of goods sold	25.2	48.7	38.2	31.8	50.3	47.6	49.4	36.7	42.0	55.1	55.4	58.2	57.0	62.6	87.7
Gross profit	74.8	51.3	61.8	68.2	49.7	52.4	50.6	63.3	58.0	44.9	44.6	41.8	43.0	37.4	12.3
Selling, general and administrative expenses:															
Selling	10.2	15.4	([1])	15.4	9.4	13.9	([1])	([1])	([1])	8.6	9.4	1.8	11.1	10.0	3.7
Advertising	6.4	5.3	([1])	3.9	5.1	5.7	([1])	([1])	([1])	5.2	6.5	.4	3.8	4.3	
Research	5.7	2.4	2.5	6.0	4.4	2.0	4.6	([1])	([1])	4.9	12.3	4.6	7.5	3.5	1.5
Administrative and general	6.0	18.4	([1])	13.0	7.9	7.0	([1])	([1])	([1])	11.4	3.3	3.9	12.6	3.4	3.2
Total	28.3	41.5	28.6	38.3	26.8	28.6	([1])	([1])	([1])	30.1	31.5	10.7	35.0	21.2	8.4
Net operating profit	46.5	9.8	33.2	29.9	22.9	23.8	([1])	([1])	([1])	14.8	13.1	31.1	8.0	16.2	3.9
Income from royalties and licenses	.3	.2	([1])	--------	1.1	--------	10.1	.4	1.0	2.2	([2])	1.2	.1	2.3	--------
Net profit before Federal taxes	46.9	9.5	33.8	29.8	23.7	24.2	([1])	([1])	([1])	14.8	13.0	32.0	8.0	17.2	3.7
Export sales included in net sales	23.4	9.0	([1])	11.9	25.4	22.7	61.9	27.5	27.3	30.2	7.8	56.0	30.0	53.3	--------

See footnotes at end of table.

TABLE 56.—*Selected financial ratios for antibiotic manufacturing, by company: 1950 to 1956*—Continued

	1950														
	1	2	3	4	5	6	7	8	9	10	12	13	14	15	16
Net sales	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Cost of goods sold	21.3	50.3	42.0	31.8	55.2	46.5	55.1	46.9	55.2	59.1	58.6	64.9	77.8	77.5	44.6
Gross profit	78.7	49.7	58.0	68.2	44.8	53.5	44.9	53.1	44.8	40.9	41.4	35.1	22.2	22.5	55.4
Selling, general and administrative expenses:															
Selling	10.6	14.6	(1)	16.8	9.0	14.6	(1)	(1)	(1)	8.8	12.3	2.0	11.2	10.1	3.9
Advertising	4.2	5.1	(1)	1.8	4.7	5.6	(1)	(1)	(1)	4.8	6.2	.5	4.0	5.0	
Research	4.5	2.1	2.7	6.1	4.0	2.0	5.6	(1)	(1)	4.8	14.8	4.6	9.1	6.8	3.9
Administrative and general	5.7	16.2	(1)	13.6	6.7	7.0	(1)	(1)	(1)	11.6	3.3	4.4	13.5	2.2	4.2
Total	25.0	38.0	29.6	38.3	24.4	29.2	(1)	(1)	(1)	30.0	36.6	11.5	37.8	24.1	12.0
Net operating profit	53.7	11.7	28.4	29.9	20.4	24.3	(1)	(1)	(1)	10.9	4.8	23.6	(15.6)	(1.6)	43.4
Income from royalties and licenses	(2)	--------	(1)	--------	.4	--------	5.7	.2	1.2	2.0	(2)	--------	.1	1.4	--------
Net profit before Federal taxes	53.7	11.6	28.7	28.0	21.5	24.4	(1)	(1)	(1)	10.0	4.8	23.1	(14.7)	(1.6)	43.4
Export sales included in net sales	15.5	11.5	(1)	7.4	33.6	21.6	65.5	32.1	25.3	34.0	(1)	60.6	36.8	57.5	--------

NOTE.—Figures in parentheses indicate losses. Other income and deductions are not shown separately but are included in net profit before Federal taxes.

[1] Not available.

[2] Less than 0.05 percent.

Source: FTC data request, 1957.

Industry ratios

Selected financial ratios for all companies shown in table 56 for each of the years 1950 through 1956 are set forth in table 57. The table is a summary financial picture of all antibiotics activities as reported by the leading manufacturers for each of the years shown.

Cost of goods sold ranged from the 50.2 percent of net sales shown in 1952 down to the 39.0 percent of 1956. Conversely, the gross profit ratio was 49.8 percent in 1952 and 61.0 percent in 1956, showing a gain in each intervening year.

The figures submitted showed a 12 percentage-point increase in selling, general, and administrative expenses during the 7-year period. In 1950 such expenses were approximately one-fourth of net sales, but since 1954 they have represented over a third. Most of the increase from 1950 to 1956 (8.7 out of 12.1 percentage points) is attributable to selling and advertising expense. The ratio of selling expense to net sales increased by nearly half, while the advertising ratio more than doubled during these years. Research expense ranged between 6 and 7 percent from 1952 through 1956, after a sharp rise in 1952. The percentage of sales devoted to administrative and general expenses showed a gradual increase, broken by a decline in 1954.

TABLE 57.—*Selected financial ratios for the antibiotics manufacturing industry: 1950 to 1956*

[This table includes all companies in table 56. Data have been allocated when allocation was not furnished by the company. Items, including income from royalties and licenses, stated as a percent of net sales]

Item	1956	1955	1954	1953	1952	1951	1950
Net sales	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Cost of goods sold	39.0	41.8	43.2	44.4	50.2	40.8	44.4
Gross profit	61.0	58.2	56.8	55.6	49.8	59.2	55.6
Selling, general and administrative expenses:							
Selling	13.9	13.8	13.7	12.4	11.7	9.0	9.4
Advertising	7.7	7.7	8.0	5.9	5.5	4.1	3.5
Research	6.7	7.0	6.7	6.3	6.2	4.2	4.4
Administrative and general	8.7	8.6	7.9	8.5	8.0	7.6	7.6
Total	37.0	37.1	36.3	33.1	31.4	24.9	24.9
Net operating profit	24.0	21.1	20.5	22.5	18.4	34.3	30.7
Income from royalties and licenses	3.2	2.7	2.1	1.8	1.7	1.4	.9
Net profit before Federal taxes [1]	26.0	22.0	20.2	22.2	19.3	34.5	30.5
Export sales included in net sales	16.4	18.3	22.6	22.0	22.3	28.0	29.0

[1] Other income and deductions not shown separately.

Source: FTC data request, 1957.

Further analysis of the data submitted indicates that net profit was 30.5 and 34.5 percent, respectively, in 1950 and 1951, then dropped to 19.3 percent in 1952 because of a marked decrease in gross profit and a sharp increase in selling, general, and administrative expenses. Although the reported gross profit rate has more than recovered in sub-

sequent years, the net profit ratios never recovered to their 1950–51 level. The continuing rise in selling, general, and administrative expenses has stood in the way, more than offsetting increased income from royalties and licenses. Income from royalties and licenses, expressed in percent of sales, has represented only a small part of total income, but has increased every year—from 0.9 percent in 1950 to 3.2 percent in 1956.

The ratios of export sales to total sales show, with the exception of 1954, a consistent decrease from a high of 29 percent in 1950 to a low of 16.4 percent in 1956. These ratios, however, do not reflect the export sales of one of the leading antibiotics producers, whose inclusion would have altered the figures and might have affected their trend.

Antibiotics group ratios

In order to avoid disclosure of individual company data, it was decided to group all antibiotics into the five following major groupings.

1. *Old forms of penicillin.*—These include (*a*) procaine penicillin, (*b*) potassium penicillin, (*c*) combinations of potassium and procaine penicillin, and (*d*) all other penicillins and combinations thereof except those called "new forms of penicillin."
2. *New forms of penicillin.*—Include benzathine penicillin, penicillin V, and hydrabamine penicillin G. These are given only for 1954–56, to avoid company disclosure.
3. *Streptomycin.*—This includes (*a*) streptomycin, (*b*) dihydrostreptomycin, and (*c*) streptoduocin.
4. *Broad spectrum.*—This category includes (*a*) tetracycline, (*b*) chlortetracycline, (*c*) oxytetracycline, and (*d*) chloramphenicol.
5. *All others.*—This comprises (*a*) bacitracin, (*b*) erythromycin, (*c*) neomycin, (*d*) novobiocin, (*e*) tyrothricin, (*f*) antibiotic combinations except those included in group 1, and (*g*) miscellaneous.

Table 58 shows selected financial ratios of group 2 for the years 1954 through 1956, and for groups 1, 3, 4, and 5 for 1950 through 1956. This table includes data from those companies in table 56 which furnished detailed information, together with data from two additional companies whose expenses had to be reallocated to put them on a comparable basis. All figures except net sales are expressed as a percentage of the total sales of its group. The figures shown opposite net sales each year reflect the percent of aggregate net sales represented by each of the groups.

TABLE 58.—*Selected financial ratios of antibiotic product groups: 1950 to 1956*

[All figures except net sales are expressed as a percent of total net sales in each group]

Item	Penicillin—Old forms	Penicillin—New forms	Steptomycin	Broad spectrum	All others
1956					
Net sales (percent of total antibiotic sales)	11.1	7.9	3.9	50.9	26.2
Cost of goods sold	70.8	21.3	110.7	24.6	45.8
Gross profit	29.2	78.7	(10.7)	75.4	54.2
Selling, general and administrative expenses:					
Selling	12.5	12 0	11.3	15.3	14.2
Advertising	6.1	8.4	5.6	9.3	6.8
Research	5.7	4.7	6.4	7.0	6.5
Administrative and general	10.5	10.2	7.4	7.0	9.3
Total	34.8	35.3	30.7	38 6	36.8
Net operating profit	(5.6)	43.4	(41.4)	36.8	17.4
1955					
Net sales (percent of total antibiotic sales)	5.0	12.9	4.7	56 1	21.3
Cost of goods sold	83.3	19.7	110.5	26 3	46.9
Gross profit	16.7	80.3	(10.5)	73.7	53.1
Selling, general and administrative expenses:					
Selling	12.7	15 5	10.3	15.8	11.6
Advertising	5.2	8.9	5.1	9.1	7.2
Research	5.8	3 2	5.9	7.0	6.8
Administrative and general	10.2	16 5	5.6	6.7	8.6
Total	33 9	44 1	26 9	38 6	34.2
Net operating profit	(17.2)	36.2	(37.4)	35.1	18.9
1954					
Net sales (percent of total antibiotic sales)	17.3	4.0	6.1	52.5	20.1
Cost of goods sold	72.1	17.4	93.5	25.9	47.7
Gross profit	27.9	82.6	6.5	74.1	52.3
Selling, general and administrative expenses:					
Selling	13.6	16.6	10.6	15.1	12.9
Advertising	5.1	7.9	5.3	9.5	10.1
Research	6.9	4.0	5.8	6.5	7.0
Administrative and general	9.7	18.8	5.7	5.6	8.6
Total	35.3	47.3	27.4	36.7	38.6
Net operating profit	(7.4)	35.3	(20.9)	37.4	13.7

Item (1953)	Penicillin—old forms [1]	Strepto-mycin	Broad spectrum	All others
Net sales (percent of total antibiotic sales)	23.3	7.2	46.0	23.5
Cost of goods sold	69.3	78.6	24.5	50.5
Gross profit	30.7	21.4	75.5	49.5
Selling, general and administrative expenses:				
Selling	11.6	9.5	13.6	12.4
Advertising	4.5	4.3	6.5	7.5
Research	5.9	5.7	6.2	6.0
Administrative and general	9.7	6.6	5.8	9.5
Total	31.7	26.1	32.1	35.4
Net operating profit	(1.0)	(4.7)	43.4	14.1

See footnote at end of table.

TABLE 58.—*Selected financial ratios of antibiotic product groups: 1950 to 1956*—Continued

Item	Penicillin—old forms [1]	Strepto-mycin	Broad spectrum	All others
	1952			
Net sales (percent of total antibiotic sales)	26.3	10.1	49.7	13.9
Cost of goods sold	78.2	75.9	26.0	54.7
Gross profit	21.8	24.1	74.0	45.3
Selling, general and administrative expenses:				
Selling	13.2	10.6	12.9	12.1
Advertising	5.5	4.6	6.8	5.3
Research	5.7	4.7	5.7	6.0
Administrative and general	10.4	4.1	4.9	10.1
Total	34.8	24.0	30.3	33.5
Net operating profit	(13.0)	.1	43.7	11.8
	1951			
Net sales (percent of total antibiotic sales)	37.4	13.3	40.1	9.2
Cost of goods sold	46.3	60.7	25.6	36.5
Gross profit	53.7	39.3	74.4	63.5
Selling, general and administrative expenses:				
Selling	11.5	6.8	9.2	11.9
Advertising	5.1	3.0	5.6	5.2
Research	4.5	3.4	4.2	4.7
Administrative and general	9.7	4.8	5.3	9.1
Total	30.8	18.0	24.3	30.9
Net operating profit	22.9	21.3	50.1	32.6
	1950			
Net sales (percent of total antibiotic sales)	44.4	13.4	35.4	6.8
Cost of goods sold	49.3	63.9	23.8	32.8
Gross profit	50.7	36.1	76.2	67.2
Selling, general and administrative expenses:				
Selling	11.4	6.2	10.4	16.5
Advertising	4.3	2.4	4.1	7.1
Research	4.2	3.7	4.0	6.3
Administrative and general	9.4	5.1	5.6	11.4
Total	29.3	17.4	24.1	41.3
Net operating profit	21.4	18.7	52.1	25.9

[1] Prior to 1954 only 1 company reported manufacturing any of the newer forms of penicillin. To avoid disclosure the data for this product of this company are not shown.

NOTE.—Figures in parentheses indicate losses.

Source: FTC data request, 1957.

A marked change in the percentage relationships of the various groups to total antibiotics sales during the period under review is apparent. For example, in 1950, sales of group 1 penicillin represented almost 45 percent of the total, and by 1956 this ratio had dropped to 11.1 percent. Since 1952 the penicillin group 1 has shown a loss at the net operating profit level. These minus figures have fluctuated rather markedly, ranging from an almost break-even point in 1953 to a minus 17.2 in 1955. The cost of goods sold increased from 46.3 cents of each dollar of sales in 1951 to 78.2 cents in 1952. The drastic change in profit ratios from 1951 to 1952 is undoubtedly a reflection of the sharp decrease in selling price at that time. The selling, general, and

administrative costs increased from 29.3 percent in 1950 to 34.8 percent in 1952, a figure which was again reported in 1956 after slight fluctuations between.

The data showed that Group 2, New Forms of Penicillin, has been the most profitable of the five groups in table 58 in 1955 and 1956. In the 3 years that it is shown separately, the cost of goods sold has been at a very low figure, about 20 percent of net sales.

The streptomycin group experienced a continuous drop with respect to its proportion of total antibiotic sales, beginning in 1952. Between 1951 and 1956 this proportion decreased from 13.4 percent of total dollar sales to 3.9 percent—although the group's share of total pounds of antibiotics production decreased only from 23.5 to 20.8 percent. In actual figures, output more than trebled, but sharp price declines reduced total dollar sales. In 1951 net operating profit amounted to 21.3 percent of sales, but in 1952 to only 0.1 percent. Net operating deficits of 4.7, 20.9, 37.4, and 41.4 percent followed in 1953–56, respectively.

It is possible that a disproportionate share of the joint costs was assigned to the streptomycins. If, however, these reported losses correctly reflect the streptomycin situation, the question arises why companies continue to manufacture products on which losses are incurred and which, in the case of streptomycin, have increased each year for 4 years. Moreover, the producers have increased their output of the streptomycins in these deficit years, from 430,000 pounds in 1953 to 641,000 pounds in 1956. Explanations given by the companies for continuing the manufacture of this seemingly unprofitable product included (1) desire to offer a full line of ethical drugs, and reluctance to withdraw a medicine needed by the public on financial grounds alone; (2) expectation that company sales would increase due to (*a*) expanding world demand, (*b*) company's increased penetration of the available market, or (*c*) the exit of competitors from the market; and (3) the expectation of success in efforts to reduce cost of production.

Quite a different picture emerges from the data for the two remaining groups: "Broad spectrum" and "All others." In 1950, when the broad spectrum antibiotics comprised 35.4 percent of total sales, the gross profit amounted to 76.2 percent and the net operating profit to 52.1 percent. In 1951, the broad spectrum group supplanted the penicillin group in first place. In 1956, the broad spectrum group comprised about half of total sales, or approximately 5 percentage points under the 1955 high of 56.1 percent. Its gross profit ratio remained at about the 75-percent level during all of the 7-year period. The net operating profit, however, declined from 52.1 to 36.8 percent between 1950 and 1956. This decrease appears

to be mainly the result of increases in selling and advertising expenses since 1954. The broad spectrum group's total selling, general, and administrative expense ratio rose from a low of 24.1 percent in 1950 to a high of 38.6 percent in 1955 and 1956. This increase of 14.5 percentage points was greater than that for these expenses in any other group.

As to the "All others" group, it may be noted that, with the exception of 1954, there was a consistent increase in its ratio to total sales, from the 6.8 percent of 1950 to the 26.2 percent of 1956. The following tabulation shows for 1950 and 1956 the proportionate amount of sales of each antibiotic represented in the "All others" group:

Antibiotic	1956	1950
Combinations	48.2	56.1
Erythromycin	20.6	----
Neomycin	7.0	----
Novobiocin	6.8	----
Bacitracin	4.3	40.6
Oleandomycin	2.2	----
Viomycin	.9	.3
Polymyxin	.7	.1
Tyrothricin	.2	1.8
Miscellaneous	9.1	1.1
Total	100.0	100.0

The above tabulation indicates that the "combinations" represent the largest percentage in each of the 2 years. The sales of combinations in 1950 comprised 1.7 percent of the $249,623,000 antibiotics net sales shown in table 55, while in 1956 they represented 12.3 percent of the $337,718,000 total for that year. Bacitracin dropped from 40.6 percent to 4.3 percent of the "all others" group, but its dollar volume remained about the same, since the total sales of the whole group increased more than tenfold. Erythromycin, not produced in 1950, accounted for slightly more than one-fifth of the total sales of this group in 1956.

The net operating profit ratio, which was 25.9 percent for the "All others" group in 1950, dropped to 17.4 percent in 1956.

Profit Comparisons

Profits compared to assets of selected antibiotics manufacturers

Usable financial data reflecting total assets devoted to the manufacture of antibiotics for each of the years 1950 through 1956 were furnished by six leading antibiotics producers. Table 59 shows the percentage of net profit before Federal taxes to such assets. In order to avoid disclosing individual company data, numbers which do not necessarily correspond to those of table 56 are used for the companies. The companies have been ranked on the basis of their 1956 ratios.

TABLE 59.—*Net profit for antibiotics operations as a percent of assets, by company: 1950 to 1956*

[Net profits are before Federal income and excess profits taxes]

Company No.	1956	1955	1954	1953	1952	1951	1950
1	57.6	42.5	29.9	28.4	5.2	13.8	23.2
2	50.9	43.0	39.9	37.1	37.9	61.5	101.2
3	22.2	6.5	0.2	4.9	(2.3)	19.3	21.1
4	17.9	18.7	15.3	19.3	18.2	37.7	31.5
5	12.6	7.8	5.1	(8.4)	2.6	36.3	19.1
6	2.0	(2.7)	(3.9)	[1] 0	(1.6)	12.2	11.7
Average	28.5	23.3	20.6	19.4	18.2	37.1	42.2

[1] Less than 0.05 percent.

NOTE.—Figures in parentheses indicate losses.

Source: FTC data request, 1957.

Company No. 2 shows the highest percent of profits to assets in each of the years with the exception of 1956, when it was second to company No. 1. Company 2 ranked among the largest in the amount of total assets devoted to antibiotics operations. Company 1, which ranks lowest in order of such assets in each of the 7 years, had rather wide differences in its profit ratio in this same period. The 1956 profit ratios ranged from a low of 2.0 percent for company 6 to a high of 57.6 percent for company 1. Significant variations also appear in many of the earlier years shown in the tabulation. One company reported a loss on its antibiotics operations in 3 years and another a loss in 1 year, while another's pretax profit ratio reached 101.2 precent in 1950. Attention is invited to the selected financial ratios set forth in table 56 for more detailed information.

Comparison of antibiotics profits with pharmaceutical and consolidated profits

Table 60 compares the ratios of antibiotics profits before Federal taxes to assets devoted to antibiotics operations for the 5 companies of table 59, for which total assets devoted to pharmaceutical operations were also available, with (1) the ratios of total pharmaceutical profits before Federal taxes to total assets devoted to pharmaceutical operations of these 5 antibiotics companies; (2) the ratios of profits before Federal taxes to total assets of the only 10 pharmaceutical companies, manufacturing predominantly ethical drugs but not antibiotics, for which financial statements were published for the years 1950–56; and (3) the profit ratios on consolidated operations of the 10 antibiotics companies publishing financial statements.

Table 61 makes these same comparisons in terms of profits expressed as a percent of net sales instead of assets, though for this comparison reported antibiotics profits of 6 instead of 5 companies were available.

TABLE 60.—*Net profits as a percent of assets for certain antibiotic and other pharmaceutical manufacturers: 1950–56*

[The 5 antibiotic companies shown in sec. I which are ranked on the basis of 1956 profit ratios are the only companies which submitted usable data for both pharmaceutical and antibiotic operations for the years 1950 to 1956. Antibiotics ratios reflect the results of sales of all grades (medicinal and nonmedicinal). The 10 companies listed in sec. II, which are ranked on the basis of 1956 profit ratios, are the only predominantly pharmaceutical manufacturers whose published financial statements are available for the period under review. The antibiotic companies shown in sec. III on a consolidated basis are listed in alphabetic order.]

Sec.	Company	1956		1955		1954		1953		1952		1951		1950	
		P.[1]	A.[1]	P.	A.	P.	A.	P.	A.	P.	A.	P.	A.	P.	A.
I	Antibiotic company: [2]														
	1	81.0	57.6	40.8	42.5	30.4	29.9	29.8	28.4	25.8	5.2	29.3	13.8	44.0	23.2
	2	34.5	50.9	29.5	43.0	27.6	39.9	26.5	37.1	23.9	32.9	43.0	61.5	55.1	101.2
	3	31.9	22.2	21.9	6.5	13.4	.2	15.6	4.9	12.2	(2.4)	23.0	19.3	27.7	21.1
	4	17.3	17.9	18.0	18.7	13.4	15.3	16.6	19.3	14.3	18.2	32.8	37.7	30.5	31.5
	5	16.8	2.0	15.1	(2.7)	16.2	(3.9)	9.4	([3])	7.0	1.6	13.1	12.2	15.3	11.7
	Weighted average (5 companies)	31.2	30.0	23.3	25.0	18.8	22.0	18.6	22.0	15.3	19.6	28.8	37.2	33.5	45.3

Sec.	Company	P.	P.	P.	P.	P.	P.	P.
II	Pharmaceutical company:							
	Smith, Kline, & French Laboratories [4]	74.5	79.5	62.7	44.6	41.2	41.0	43.5
	Stuart Co. [4]	51.2	40.8	40.0	40.3	46.6	49.3	49.5
	G. D. Searle & Co.	50.4	52.9	58.2	67.0	68.3	83.7	67.6
	Schering Corp.	50.0	53.3	17.7	20.1	22.4	20.1	22.7
	Norwich Pharmacal Co.	31.8	30.0	26.1	25.0	24.0	21.9	23.1
	Lakeside Laboratories Inc.	31.0	27.4	23.4	32.7	17.2	19.4	20.0
	Allied Laboratories Inc.	27.0	16.0	13.5	13.8	9.9	15.5	19.9
	Mead Johnson & Co.	25.8	20.8	20.2	17.8	17.3	18.6	15.3
	Sterling Drug, Inc.	23.4	23.2	20.6	20.4	20.0	21.8	22.0
	Baxter Laboratories, Inc.	13.1	13.3	12.6	17.3	23.8	19.1	27.8
	Weighted average (10 companies)	37.5	36.4	28.1	26.1	25.4	26.8	26.3

Sec.	Company	C.[1]	C.	C.	C.	C.	C.	C.
III	Antibiotic company (consolidated):							
	Abbott Laboratories	20.2	19.0	17.0	18.3	16.5	21.2	24.3
	American Cyanamid	15.2	14.5	10.2	11.8	11.1	22.3	21.4
	American Home Products	39.4	29.7	26.6	25.2	21.6	23.2	22.7
	Bristol-Myers	18.5	15.3	12.2	9.2	9.0	25.6	19.2
	Commercial Solvents	8.3	8.1	7.2	7.2	3.5	19.7	19.7
	Eli Lilly	30.4	21.2	14.1	15.1	13.3	23.7	28.9
	Merck & Co.	24.5	22.7	18.0	17.0	24.6	37.9	40.8
	Olin Mathieson	12.1	13.3	12.8	13.4	8.6	15.5	18.2
	Parke, Davis	25.5	23.1	17.2	16.4	28.5	41.0	36.4
	Chas. Pfizer	21.3	18.9	18.0	20.8	17.0	34.6	32.0
	Weighted average (10 companies)	19.3	17.1	14.2	15.0	14.4	25.9	25.7

[1] P.—pharmaceutical operations; A.—antibiotic operations; C.—consolidated operations (entire business in all lines as reported in published financial statement).

[2] The 5 antibiotic companies shown accounted for approximately 55 to 60 percent of total antibiotic sales in 1950 and approximately 70 to 75 percent in 1956.

[3] Less than .05 percent.

[4] These companies have wholesaling subsidiaries. Normally wholesaling operations tend to yield a higher ratio of profits to assets and a lower ratio of profits to sales than do manufacturing operations.

Parentheses indicate losses.

Source: FTC data request, 1957, and Moody's Industrial Manual.

TABLE 61.—*Net profits as a percent of sales for certain antibiotic and other pharmaceutical manufacturers: 1950–56*

[The 6 antibiotic companies shown in sec. I, which are ranked on the basis of 1956 profit ratios, are the only companies which submitted usable data for both pharmaceutical and antibiotic operations for the years 1950 to 1956. Antibiotics ratios reflect the results of sales of all grades (medicinal and nonmedicinal). The 10 companies listed in sec. II, which are ranked on the basis of 1956 profit ratios, are the only predominantly pharmaceutical manufacturers whose published financial statements are available for the period under review. The antibiotic companies shown in sec. III on a consolidated basis are listed in alphabetic order.]

Sec.	Company	1956		1955		1954		1953		1952		1951		1950	
		P.[1]	A.[1]	P.	A.	P.	A.	P.	A.	P.	A.	P.	A.	P.	A.
I	Antibiotic company: [2]														
	1	35.2	32.3	22.4	26.8	17.9	20.8	18.3	21.2	16.3	4.1	15.7	9.5	19.4	11.6
	2	29.7	40.5	28.0	37.9	27.9	39.7	28.5	42.0	24.7	37.9	35.3	46.9	40.7	53.7
	3	36.3	30.3	25.5	11.1	18.9	.4	23.3	10.1	18.4	(3.9)	27.7	23.7	31.2	21.5
	4	27.3	15.1	26.0	8.2	24.1	10.0	24.3	30.9	23.6	29.7	27.7	29.8	31.0	28.0
	5	15.2	19.3	15.5	22.5	12.2	22.5	17.5	27.6	15.3	27.2	38.1	48.4	31.7	41.0
	6	12.4	1.8	11.8	(2.8)	12.5	(4.2)	9.4	([3])	8.9	(2.3)	15.2	14.8	13.1	10.0
	Weighted average (6 companies)	26.7	26.4	22.0	23.3	19.5	23.4	21.2	27.2	18.5	22.8	28.9	37.5	29.9	35.4

Sec.	Company	1956 P.	1955 P.	1954 P.	1953 P.	1952 P.	1951 P.	1950 P.
II	Pharmaceutical company:							
	Smith, Kline, and French Laboratories [4]	39.0	38.0	31.1	23.7	23.1	22.1	23.4
	Stuart Co.[4]	27.0	22.6	19.9	19.7	22.0	24.4	22.8
	G. D. Searle & Co	48.7	49.7	50.6	51.1	50.2	54.4	50.0
	Schering Corp	41.7	41.5	16.5	17.6	19.0	18.5	17.2
	Norwich Pharmacal Co	23.4	23.1	20.1	18.8	17.6	18.1	18.2
	Lakeside Laboratories Inc	17.1	14.2	11.5	16.0	19.8	11.7	11.9
	Allies Laboratories Inc	24.3	14.9	13.1	12.7	9.3	13.9	16.2
	Mead Johnson & Co	19.6	16.7	16.5	15.2	15.5	17.6	14.9
	Sterling Drug, Inc	18.7	18.3	16.4	15.8	15.8	17.1	17.6
	Baxter Laboratories Inc	9.4	9.9	7.6	9.1	14.6	12.6	16.9
	Weighted average (10 companies)	27.8	26.6	20.9	19.2	19.1	20.4	20.4

Sec.	Company	C.[1]	C.	C.	C.	C.	C.	C.
III	Antibiotic company (consolidated):							
	Abbott Laboratories	21.4	20.4	18.8	19.5	18.1	23.9	25.7
	American Cyanamid	17.0	16.6	12.8	13.8	12.7	21.4	21.6
	American Home Products	22.6	18.4	17.0	16.4	13.7	13.5	14.2
	Bristol-Myers	11.9	11.7	11.2	8.9	8.7	20.9	15.7
	Commercial Solvents	10.5	10.4	9.9	9.8	4.7	18.6	19.0
	Eli Lilly	34.3	24.0	18.9	21.3	18.7	27.2	31.3
	Merck	23.9	22.1	18.3	15.7	17.2	28.4	23.9
	Olin Mathieson	13.3	14.7	12.9	14.3	14.6	24.1	21.9
	Parke, Davis	26.4	23.3	17.4	16.2	25.9	34.6	31.3
	Chas. Pfizer	18.2	16.2	15.8	20.4	18.1	40.2	32.9
	Weighted average (10 companies)	19.1	17.4	14.8	15.7	15.5	24.5	23.2

[1] P.—pharmaceutical operations; A.—antibiotic operations; C.—consolidated operations (entire business in all lines as reported in published financial statement).

[2] The six antibiotic companies shown accounted for approximately 60 to 65 percent of sales in 1950 and approximately 75 to 80 percent in 1956.

[3] Less than 0.05 percent.

[4] These companies have wholesaling subsidiaries. Normally wholesaling operations tend to yield a higher ratio of profits to assets and a lower ratio of profits to sales than do manufacturing operations.

Parentheses indicate losses.

Source: FTC data request, 1957, and Moody's Industrial Manual.

The asset comparisons yielded the following results.

(1) Two of the five antibiotics companies included showed a lower profit ratio for their antibiotic than for their pharmaceutical operations in all 7 years; one showed a lower antibiotic ratio in all years but 1955; and two showed a higher antibiotic ratio each year. The five-company weighted average profit ratio on antibiotics operations was higher than that on pharmaceutical operations in every year but 1956. The advantage was being steadily whittled down during these years from 11.8 percentage points in 1950 to 1.7 percentage points in 1955 and, as stated, the pharmaceutical profits were higher in 1956.

(2) The average profit ratio of the 10 pharmaceutical companies used for comparison was lower than both the antibiotic and the pharmaceutical profit ratio of the 5 companies in the first 2 years, 1950 and 1951, and higher than both these ratios from 1952 through 1956. Three of the 10 pharmaceutical companies had exceptionally high profit ratios throughout, and a fourth had such a ratio in the two most recent years. Two of these four have wholesaling subsidiaries, and the relatively low ratio of assets to sales in the wholesaling business might tend to exaggerate the profit ratio of wholesalers compared to that of manufacturers if computed on the basis of assets.

(3) The comparison with published consolidated financial data of the 10 antibiotics companies shows that both the average antibiotic profit ratio and the average pharmaceutical profit ratio of the antibiotics companies ran well above the average consolidated profit ratio in each of the 7 years. This indicates that for the antibiotics manufacturing companies, the manufacture and sale of products other than antibiotics and total pharmaceuticals is, on the whole, significantly less profitable. It is impossible to match the profit ratios company by company without disclosing the identity of the numbered companies. The consolidated profit ratios are also lower each year than those of the 10 pharmaceutical companies used for comparison.

The comparisons of rates of profit before Federal taxes with respect to net sales, shown in table 61, disclosed relationships similar to those with respect to total assets.

(1) Two companies reported lower antibiotic than pharmaceutical profit ratios in each of the 7 years, 2 reported lower antibiotic profit ratios in 4 years, and 2 reported higher antibiotic ratios each year.

(2) The average ratio of profit to sales of the 10 pharmaceutical companies chosen for comparison was considerably lower than either the average antibiotic profit ratio or the average pharmaceutical profit ratio of the antibiotics companies in 1950 and 1951. It was between these two ratios in 1952 and again in 1954; and exceeded both of these ratios by more than 3 percentage points in 1955 and by more than 1 percentage point in 1956. The profits made by Schering Corp. on two steroid hormones used to combat arthritis and certain other diseases and by Smith, Kline & French on its tranquilizers were important factors in the gain in profits of these other companies after 1954. In this comparison of profits with respect to sales, the fact that Smith, Kline & French and Stuart Co. have wholesaling subsidiaries lowers the average profit ratio of the group, since wholesaling generally yields a lower return on sales than does manufacturing.

(3) Once again, the average antibiotic and pharmaceutical profit ratios of the antibiotics companies exceeded their average consolidated profit ratios in every year. In other words, with respect to sales as well as to assets, their pharmaceutical operations were on the average the most profitable part of their business.

Graphic analysis of antibiotic and pharmaceutical profits

A 7-year comparison of profits before Federal taxes from antibiotic operations with the overall pharmaceutical business of six companies is shown in chart 8. The numbers used to avoid disclosing the manufacturers' identity are those used in table 61, and the graph merely illustrates section 1 of that table.

In each of the years from 1950 through 1956, the antibiotic profit ratio of companies 2 and 5 exceeded their total pharmaceutical profit ratio. Companies 3 and 6, however, had higher profit ratios for their total pharmaceutical operations throughout the 7-year period. Company 6 had losses in antibiotics from 1952 through 1955, and company 3 sustained a loss in antibiotics in 1952. Antibiotic profits ratios of companies 1 and 4 were below their pharmaceutical profit ratios in 4 out of the 7 years.

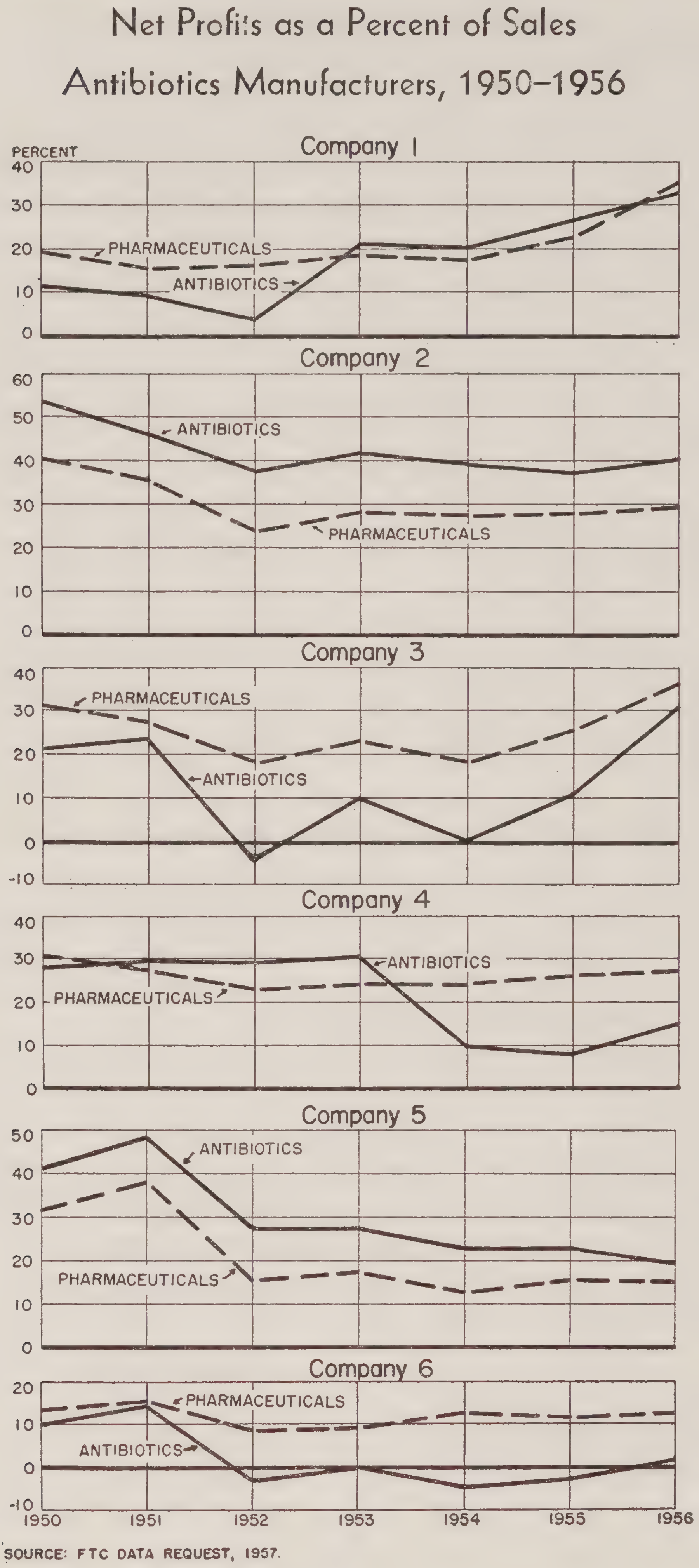
Net Profits as a Percent of Sales
Antibiotics Manufacturers, 1950–1956
Company 1
PERCENT
PHARMACEUTICALS
ANTIBIOTICS
Company 2
ANTIBIOTICS
PHARMACEUTICALS
Company 3
PHARMACEUTICALS
ANTIBIOTICS
Company 4
ANTIBIOTICS
PHARMACEUTICALS
Company 5
ANTIBIOTICS
PHARMACEUTICALS
Company 6
PHARMACEUTICALS
ANTIBIOTICS
1950
1951
1952
1953
1954
1955
1956
SOURCE: FTC DATA REQUEST, 1957.

CHART 8.

Comparison with profits in all manufacturing industries and in chemical industry

The following tabulation shows the percentage of net profits before Federal taxes to assets for all manufacturing industries, chemicals and allied products, and antibiotics for the years 1950 through 1956:

Years	All manufacturing industries (except newspapers)	Chemical and allied products	Antibiotics
1956 [1]	14.6	18.3	28.5
1955	15.7	19.1	23.3
1954	12.2	15.1	20.6
1953	14.4	16.2	19.4
1952	14.1	16.5	18.2
1951	18.8	22.3	37.1
1950	19.6	24.0	42.2

[1] Profits for a group called "Drugs and Medicines" are available in the FTC-SEC reports since April 1956. The ratios for the quarters through March 1957 were 24.7, 27.4, 24.2, and 27.9 percent.

The "all manufacturing" and "chemicals and allied products" ratios were computed from the Quarterly Financial Report for Manufacturing Corporations published by the Federal Trade Commission and the Securities and Exchange Commission. These quarterly data were not intended to be additive for arriving at annual totals, but for the purpose of this tabulation, annual estimates were made by adding the quarterly profits and averaging quarterly assets. The antibiotics ratios are from table 59, and are applicable only to that segment of the business of each of the six companies included.

It is clear that the rate of return on assets was greater for the antibiotics industry than for either of the other two broader industry groups in each of the years shown. It was also 2 or 3 points higher than that for "drugs and medicines" in the one year for which that series is available.

It should be noted that the manufacture of antibiotics, like the manufacture of all drugs and medicines, is subject to certain inherent risks. One is the risk of obsolescence of any or all of its products, if they lose their potency due to the development of immunity or if still more effective remedies, or equally effective but cheaper remedies, are discovered. Another is the manufacturer's product liability, under which he may become the defendant in large damage suits.

The higher rate of profit in antibiotics is most pronounced in 1950 and 1951, and 1956. A comparison of tables 57 and 58 indicates that this may have resulted in part from the situation in the penicillin and streptomycin groups. These products yielded substantial profits in 1950 and 1951. As output expanded due to increased facilities and increased yield, their prices dropped sharply, and remained through 1956 at a level which was unprofitable for some of their producers. There was, however, a price recovery in the latter part of 1956.

The excess of antibiotic profits over all chemical profits ranged between 1.7 and 18.2 percentage points, being lowest in 1952 and highest in 1950. The chemical industry ratio, in turn, has ranged from 1.8 to 4.4 percentage points higher than that for all manufacturing, in 1953 and 1950, respectively. The antibiotic ratios exceeded that for all manufacturing by from 4.1 to 22.6 percentage points. In 1950, 1951, and 1956, it was approximately twice the average ratio for all manufacturing.

CHAPTER VIII

Patent Ownership and Licensing in the Antibiotics Industry

Introduction

Research programs of companies engaged in the manufacture and sale of antibiotics are directed toward the discovery and development of new products and processes of manufacture and improvements thereon which can be patented. The results of these research programs have much to do with success, or even survival, in the antibiotics industry. The more successful companies have either patented one or more useful antibiotic products for which there is great medical demand; or they have obtained licenses to produce and sell such antibiotics from other companies which hold patents. Many of these licenses result from interference settlements between companies having competing applications for the same discovery pending in the Patent Office. In any event, whether patents are obtained, or whether licenses are obtained, such results are directly attributable to research activities.

This chapter is divided into four sections. In each section an effort has been made to focus attention on some particular aspect of patent relationships among manufacturers of antibiotics and to discuss the manner in which these relationships have affected the production and distribution of antibiotics. These sections are entitled:

- Product Patents in the Antibiotics Industry.
- Patent Ownership in the Antibiotics Industry.
- Patent Licensing in the Antibiotics Industry.
- Significant Patent Litigation: (*a*) Procaine penicillin, (*b*) tetracycline

Of necessity, there is some overlapping of subject matter between the "Patent Ownership" and the "Patent Licensing" sections, but this has been held to a minimum.

The United States Constitution provides that "The Congress shall have power * * * to promote the progress of science and the useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries."[1] The

[1] U. S. Constitution, art. 1, sec. 8.

means chosen by the first United States Congress, in 1790, to implement this constitutional mandate was the establishment of a patent system.[2] It has remained a cornerstone of our national policy, represented at present by the Patent Code of 1952.[3] The working of this system has been described by one Federal court as follows:

> The patent system encourages invention not only in that it rewards the inventor with a patent, but it spurs the competitiors to put forth their mightiest effort to produce a product as good, yet different from the patentee's * * *. It must be admitted that in an effort to avoid infringement of a patent, as much skill is often displayed as is shown in the conception or development of invention itself. There is, however, nothing objectionable in this. In fact, it is thus that the patent system is working at its best. For it is then that we have competition between a holder of a legal monopoly and his competitors. It illustrates how the legal monopoly evidenced by a patent excites the competitors to their best to meet or excel the product covered by the existing patent. Competition among industrial rivals and inventors is thus incited.[4]

It will be apparent later in this chapter that there has been a strong impetus to research and development in the antibiotics industry as a result of the competition among rival pharmaceutical houses in the race to obtain patents on individual antibiotic products. In a line of cases dating back to 1830, the United States Supreme Court has consistently held that the reward to inventors is merely a means to the end of attaining the "main object" of the patent system, which is "to promote the progress of science and the useful arts."[5] A corollary principle has been repeatedly enunciated by the Supreme Court: "It is the public interest which is dominant in the patent system * * *. It is the protection of the public in a system of free enterprise which alike nullifies a patent where * * * it is invalid * * * and denies to the patentee after issuance the power to use it in such a way as to acquire a monopoly which is not plainly within the terms of the grant."[6]

In former times it was assumed that the principal effect of patent grants would be to stimulate individual inventors to devote "sacrificial days" to the invention and development of new products. But in the modern industrial society of the United States, according to an authority on patent law, "the spotlight has shifted to the salaried scientist and engineer engaged in group research of the kind that accounts for the sustained whirlwind pace of current technical progress."[7] The accuracy of this statement, as applied to the anti-

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[2] 1 Stat. 109.

[3] 66 Stat. 792.

[4] *James P. Marsh Corp.* v. *United States Gauge Co.*, 129 F. 2d 161, 164, 165 (7th Circuit 1942).

[5] *Pennock* v. *Dialogue*, 2 Peters 1, 19 (1830).

[6] *Mercoid Corp.* v. *Mid-Continent Investment Co.*, 320 U. S. 661, 665 (1944).

[7] George E. Frost, "The Patent System and the Modern Economy," Study No. 2, Subcommittee on Patents, Trademarks and Copyrights of the Committee on the Judiciary, U. S. Senate, 84th Cong., 2d sess., Washington, 1957, p. 1.

biotics industry, is shown by the fact that more than 91 percent of all antibiotics patents issued during 1942–56 were granted to domestic and foreign corporations as assignees of employee inventors. Only 2½ percent of patents issued were granted to private inventors. Approximately 5 percent were issued to agencies or departments of the United States Government. Less than 2 percent were issued to research foundations and State and local governments. (See table 62.)

The patent grant is essentially a contract between inventor and Government.[8] According to the Patent Code, a patent "has the attributes of personal property."[9] The important thing, however, is the right of the patentee to exclude others from practicing the invention, if that invention meets the legal standard of patentability.

TABLE 62.—*Ownership of antibiotics patents issued: 1942 to 1956*

Owner	Antibiotics patents	
	Number	Percent of total
Domestic corporations	576	85.9
Foreign corporations	35	5.2
Total assigned to corporations	611	91.1
Individuals	17	2.5
U. S. Government	34	5.1
Others (research foundations, States, municipalities, etc.)	9	1.3
Total	671	100.0

Source: Compiled by the Federal Trade Commission from Patent Office classification files. Patents covering certain combinations of antibiotics with other drug products are not included in this table.

Product Patents in the Antibiotics Industry

An analysis of patent relations in the antibiotics industry must start with recognition of the fact that antibiotics are medical products which derive economic value from their efficiency in controlling disease-causing organisms within the human body. In some cases, only one antibiotic may be used in the treatment of a certain disease, since the organism causing the disease is not affected by any other type of antibiotic.

Some of the important antibiotics hereinafter discussed are closely related chemically and have similar effects on many disease-causing organisms. There is, therefore, the possibility of product competition between antibiotics which are substitutable in this manner. In these cases the decision as to which antibiotic to prescribe lies within the discretion of individual physicians, based upon their knowledge of the probable reactions of individual patients if one or the other of the various antibiotics is prescribed.

[8] S. Chesterfield Oppenheim, Cases on Federal Antitrust Laws, St. Paul: West Publishing Co., 1948, p. 472.
[9] 35 U. S. C., § 261, 1952.

There are many types of penicillin. Some of these types possess unique qualities in the treatment of disease. There are at least four chemically different products comprised within what was patented as "streptomycin," and apart from this there is a slightly different molecule with slightly different properties known as dihydrostreptomycin.

Four separate antibiotics are usually spoken of as the broad spectrum antibiotics: tetracycline, oxytetracycline, chlortetracycline, and chloramphenicol. Chloramphenicol stands somewhat apart from the other three members of this category in that it is characterized by a radically different chemical structure from the chemical structures of the three tetracyclines.

One additional antibiotic, erythromycin, has been of sufficient commercial importance in recent years to warrant discussion of patent arrangements relating to its production and marketing.

This discussion, therefore, will be limited to the penicillins, the streptomycins, the broad spectrums, and erythromycin.

The importance of patents covering antibiotic products

In a memorandum published in November 1954, Bristol Laboratories, Inc., explained:

> In the United States, patents are obtainable upon new drug products as well as upon processes of manufacture, and * * * product patents have, in the past, proven highly important in the drug industry Accordingly, considerable emphasis is laid in the United States upon obtaining patents upon new products.[10]

Thus, product patents in the antibiotics industry are probably more important than patents covering processes of manufacture. If a company or individual obtains a patent on a basic antibiotic product such as oxytetracycline (Terramycin), or chlortetracycline (Aureomycin), it has to right to *exclude* all others from making, using, or selling this product. If a license under a basic product patent cannot be obtained by other companies, they may not make that product at all, and cannot use or sell it unless they first purchase it from the source manufacturing it under the patent. Some basic antibiotic product patents have been widely licensed; others have been licensed to a limited extent; and a few important ones have not been licensed.

Penicillin

As previously noted, no patent protection on this product was obtained. Production of the basic forms of penicillin has, therefore, never required a license from a patent owner. Several of the most important steps and methods in the fermentation process for production of penicillin were patented by the United States Department of Agri-

[10] Memorandum re "Tetracycline Patent Situation in the United States," Bristol Laboratories, Inc., New York, November 1, 1954.

culture, which followed the policy of licensing all applicants under these patents on a royalty-free basis. As a consequence, many companies entered into the penicillin business during the late 1940's, the years when penicillin production boomed. Since 1950 several patents have been obtained on new chemical types of penicillin; for example, procaine penicillin,[11] benzathine penicillin, and phenoxymethyl penicillin. As more fully considered later in this chapter, procaine penicillin has been widely licensed as a result of several factors, including interference settlement agreements, contractual obligations of the patentee, Lilly, settlement of lawsuits, and Lilly's policy of licensing this patent to other competitors. The benzathine penicillin products patent owned by Wyeth Laboratories has been licensed to three companies which were parties to an interference settlement agreement relating to this product. Lilly also owns a product patent covering phenoxymethyl penicillin which, so far as is known, has been licensed by Lilly to one company, Wyeth Laboratories.

Streptomycin

Entry into the streptomycin market was free of restrictions, although for different reasons. Streptomycin was discovered by Dr. Selman A. Waksman and his student, Dr. Albert Schatz, two microbiologists doing research at Rutgers University. Under the terms of a contract with Merck & Co., Merck had exclusive rights to exploitation of all patentable scientific discoveries by Dr. Waksman resulting from research subsidized by Merck. It was in the course of this research that streptomycin was discovered.

When the importance of streptomycin became apparent as a result of extensive chemical, clinical, and pharmacological testing, Dr. Waksman requested Merck & Co. to give up its exclusive contract rights to exploit streptomycin commercially. In compliance with this request, Merck & Co. assigned its streptomycin product patent rights to a nonprofit research foundation organized at Rutgers. The patent was issued to the foundation in 1948. In return Merck was granted a nonexclusive license to make, use, and sell streptomycin, providing for the payment by Merck to the foundation of a royalty based on a percentage of net sales of streptomycin by Merck. Subsequently the foundation granted similar licenses to other pharmaceutical houses desiring to manufacture and sell streptomycin. The first $500,000 of Merck's royalties was cancelled, in partial reimbursement for its expenses in the development of streptomycin not incurred by competitors.

Approximately 18 months after the discovery of streptomycin, scientists employed in Merck's own research laboratories discovered dihydrostreptomycin, a product with very similar antibiotic activity to

[11] Procaine has been in use for many years as an anesthetic.

that of streptomycin. For some medical purposes, streptomycin proved to be preferable to dihydrostreptomycin; for others the contrary is true. Within certain limits these two antibiotics may be regarded as competitive, although as a result of slightly different toxic effects the two are frequently used in combination. The patent on dihydrostreptomycin was issued to Merck in 1950. Merck has followed a policy of licensing competitors to make, use, and sell dihydrostreptomycin. At least eight licenses have been granted to competitors, each providing for payment to Merck of a royalty based upon a percentage of each licensee's net sales of dihydrostreptomycin. Two of these licenses were obtained as a consequence of an interference settlement agreement involving Merck, Squibb, and Parke, Davis.

Prior to 1950 ease of entry into the penicillin market and ease of entry into the streptomycin-dihydrostreptomycin market existed in the antibiotics industry. This was an important factor in the development of price competition among the producers of streptomycin and dihydrostreptomycin, as well as among the producers of procaine penicillin. No restrictions existed with respect to production of sodium and potassium penicillin, as far as can be determined.

On March 25, 1950, Mr. John McKeen, presdient of Chas. Pfizer & Co., Inc., was reported to have stated, "If you want to lose your shirt in a hurry, start making penicillin and streptomycin." [12] Thirteen companies producing penicillin had made competition so keen that an amount of penicillin (100,000 units) which in 1943 sold for $20, was selling for 4½ cents at the manufacturers level in 1950.[13] In the same year streptomycin was characterized as "distress-merchandise," with production running "200 percent to 300 prcent above domestic demand." [14]

Business Week magazine summarized the situation in the antibiotics industry as follows:

> The trouble is—from a competitive point of view—that nobody goes out of business. And that is partly because nobody knows what's going to happen tomorrow. A company which is struggling along now in penicillin may come up with a better method of administering it, or a new way of making it.
>
> But there is a bigger reason for everyone wanting to hang on. That is the hope that the scores of researchers working in every company's laboratory can come up with an antibiotic it can patent as it own.[15]

At about the same time, Mr. McKeen, speaking before a group of security analysts, made the following statement:

> From the preceding analysis it is apparent that neither penicillin nor streptomycin furnishes any real indication of the outlook for the antibiotic industry. From a profit point of view, and that is what I believe you gentlemen are pri-

[12] Business Week, March 25, 1950, p. 26.
[13] Ibid.
[14] Ibid.
[15] Ibid., p. 28.

marily interested in, the only realistic solution of this problem lies in the development of new and exclusive antibiotic specialties. This as I have previously indicated is an exceedingly costly and vigorous alternative; nonetheless, it is the avenue of approach being most extensively explored by certain antibiotic houses today. This is the approach being followed by Pfizer.[16]

The four broad spectrum antibiotics

Three companies had succeeded in patenting such products by midsummer of 1950. Each company had developed an antibiotic which it could market as its own. Patents on chlortetracycline (Aureomycin), oxytetracycline (Terramycin), and chloramphenicol (Chloromycetin) had been assigned to American Cyanamid Co., Chas. Pfizer & Co., and Parke, Davis & Co., respectively; none of the companies granted any licenses permitting competitors to manufacture and sell these products.

Chlortetracycline (Aureomycin) was first marketed by American Cyanamid Co. on December 1, 1948. Since the issuance of U. S. Patent 2,482,055 on September 13, 1949, covering this antibiotic,[17] American Cyanamid Co. has had the exclusive legal right to make, use, and sell Aureomycin. In 1954 and 1955 Cyanamid negotiated cross-licensing agreements with Pfizer and Bristol respectively. These agreements do not permit the marketing by Bristol or Pfizer of a product which could be sold by druggists as chlortetracycline (Aureomycin). They merely authorize the two companies to make and use chlortetracycline to the extent necessary to make and sell tetracycline.

A patent on chloramphenicol (Chloromycetin) was issued to Parke, Davis & Co. on October 4, 1949.[18] Parke, Davis & Co. has never granted any licenses permitting competitors to manufacture and sell chloramphenicol.

It was reported that Chas. Pfizer & Co., in developing Terramycin, managed to "set something of a speed record among antibiotics." [19] A team of bacteriologists, virologists, pharmacologists, biochemists, microbiologists, analytical chemists, and chemical engineers proceeded to do in a matter of months for Terramycin what had taken "15 years in the case of penicillin and 3 years in the case of streptomycin." [20]

Procedures have been established in the Patent Office to accelerate action on pending applications, where a special need can be estab-

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[16] John E. McKeen, "Antibiotics and Pfizer & Co.," Armed Forces Chemical Journal, vol. III, No. 8 (April 1950), pp. 37–38.

[17] U. S. Patent No. 2,482,055, issued September 13, 1949, to Benjamin N. Duggar, assignor to American Cyanamid Co.

[18] U. S. Patent No. 2,483,885.

[19] Scientific American, vol. 183, July 1950, p. 29.

[20] Chemical Engineering, November 1950, p. 162.

lished.[21] Under such procedure, an affidavit executed by President John E. McKeen, of Chas. Pfizer & Co. on February 20, 1950, was submitted to the Patent Office.[22] This affidavit stated in part: [23]

> Charles Pfizer & Co., has spent large sums of money in the research and development that led to the new antibiotic disclosed in the aforesaid patent application Serial No. 129,868 and is now spending such sums on the most thorough clinical testing of said antibiotic. It must decide in the near future whether to devote a substantial part of its facilities to the production of the new antibiotic and to invest heavily in additional equipment to meet the estimated total market demand and to expend the large sums of money involved in the distribution and promotion effort inherent in selling such large quantities of this new drug. One of the most important factors influencing such decision is whether or not claims will be allowed in the above-entitled patent application that will adequately protect the additional investment required to manufacture and sell large quantities of said antibiotic. Chas. Pfizer & Co., Inc., will not enter into such a large-scale manufacturing and distributing program unless it is certain that adequate patent protection will be obtained.

Pfizer's petition was granted April 12, 1950, and on June 20, 1950, Pfizer was notified that a patent would be allowed on the application.[24] The Terramycin patent (No. 2,516,080) was issued on July 18, 1950, and assigned to Chas. Pfizer & Co., Inc. However, marketing of Terramycin was commenced by Pfizer as early as April 1, 1950.[25]

By November of 1953, largely as a result of what has been termed "an mazing coincidental discovery of the same substance," [26] four different pharmaceutical houses had filed patent applications on the product which became the fourth and most important broad spectrum antibiotic, tertcycline. These four companies were Chas. Pfizer & Co., Inc.; American Cyanamid Co.; Bristol Laboratories, Inc.; and the Heyden Chemical Corp. The importance of this situation for broad spectrum antibiotics producers was indicated by John E. McKeen, president of Chas. Pfizer & Co., Inc., in an address before a group of security analysts, in which he was quoted as stating, "It is difficult to say how long it will be before the tetracycline difficulty is resolved, and in the interim other companies may come in. But if the patent accrues to us . . . we will make very determined objections to entry of other firms than those presently in the field." [27]

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[21] Rules of Practice of the U. S. Patent Office, September 1955, Rule 102.

[22] Affidavit dated February 20, 1950, executed by John E. McKeen, president of Chas. Pfizer & Co. This affidavit is included in the patent file of U. S. Patent No. 2,516,080, "Terramycin and Its Production." As a result of special treatment afforded Pfizer's Terramycin application, only a little over 7 months was required from the date of application until the date of issuance of this patent, compared with 3½ years required for issuance of the average patent.

[23] U. S. Patent File No. 2,516,080, "Terramycin and Its Production," affidavit dated February 20, 1950, executed by John E. McKeen, president of Chas. Pfizer & Co., Inc.

[24] U. S. Patent File No. 2,516,080, Notice of Allowance, dated June 20, 1950.

[25] FTC data request, 1956.

[26] Harry F. Dowling, "Tetracycline," Medical Encyclopedia, Inc., New York, 1955, p. 7.

[27] Drug Trade News, Feb. 15, 1954. Since the first tetracycline interference (settled in January 1954) involved only Pfizer and Cyanamid, apparently Mr. McKeen's reference to "those presently in the field" meant Pfizer and Cyanamid.

After purchasing the antibiotic interests of Heyden Chemical Corp.,[28] including Heyden's tetracycline patent application, American Cyanamid agreed to a cross-licensing procedure with Chas. Pfizer & Co. "whereby no matter which got the patent they would both manufacture tetracycline."[29] Since Pfizer owned the Terramycin product patent and Cyanamid the Aureomycin product patent, and neither had granted licenses to make and sell either product, it was possible that control of the production and distribution of broad spectrum antibiotics could be maintained by Pfizer and Cyanamid, along with Parke, Davis, if either Pfizer or Cyanamid could acquire the tetracycline product patent. The facts relating to issuance of the tetracycline product patent, subsequent litigation, and its settlement by licensing are considered in a later section of this chapter.

Erythromycin

United States Patent No. 2,693,899, which discloses the product erythromycin, is owned by Eli Lilly & Co. This patent was issued on September 29, 1953, title passing immediately to Eli Lilly & Co. as assignee of the inventor. Erythromycin is not a broad spectrum antibiotic, but its annual dollar sales are approximately equal to annual dollar sales of chloramphenicol and chlortetracycline(for medicinal purposes).

Two companies, Abbott Laboratories and The Upjohn Co., are licensed under the product patent. They are entitled to licenses under all erythromycin patents obtained on applications filed prior to July 18, 1957 (relating to antibiotic cultures known on July 18, 1952), under provisions of a very extensive cross-licensing arrangement among Lilly, Abbott, and Upjohn dating back to the World War II penicillin synthesis research program sponsored by the Office of Scientific Research and Development. (Parke, Davis participated in this arrangement for a time, but dropped out prior to the end of 1948.) Cross-licensing between the three was originally restricted to patents obtained on penicillin, streptomycin, and streptothricin. On August 31, 1948, they agreed "to exchange information resulting from their joint and several research projects relating to all antibiotic substances * * *."[30] A further provision of this agreement was as follows:

> Each party hereby grants to each of the other parties hereto a nonexclusive, irrevocable, nonassignable, and royalty-free license under any and all United

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[28] Chemical Week, vol. 73, November 14, 1953, p. 15.

[29] Drug Trade News, March 15, 1954.

[30] Agreement dated August 31, 1948, between Abbott Laboratories, Eli Lilly & Co., and The Upjohn Co., and supplied to the Federal Trade Commission in response to FTC data request, 1956. Quotations from this agreement appearing hereinafter in this chapter are from this source.

States or foreign patents which any party does now or may hereafter own or control or have the right to grant licenses under, on penicillin, streptomycin, streptothricin, and any and all other antibiotic substances.

This agreement applied to all patent applications filed prior to July 18, 1957, involving antibiotic material "based on or resulting from information known or cultures existing on July 18, 1952." Since cultures of micro-organisms which produce erythromycin were known by Lilly to exist prior to July 18, 1952, Upjohn and Abbott were entitled to licenses under all patents resulting from applications pertaining to erythromycin filed by Lilly prior to July 18, 1957. Conversely, under the agreement Lilly is entitled to licenses under all patents obtained from applications filed by Abbott and Upjohn during the prescribed period. Except for these licenses each party was to maintain individual control over all patents owned by such party, with an express proviso that "no party in so controlling its said patents shall refuse to grant licenses * * * to qualified applicants (not parties hereto) upon reasonable terms, nor shall any such parties so control such patents in violation of law."

Erythromycin has been reported to be one of the most effective antibiotics presently known for combating staphylococcal infection. It was further reported that the micro-organism causing this infection has become increasingly resistant to penicillin, streptomycin, and the tetracyclines. Thus, erythromycin is useful in combating disease-causing micro-organisms against which the penicillins, streptomycins, and tetracyclines are ineffective.[31] Moreover, it is said to be competitive with other antibiotics to a considerable extent.

Patent Ownership in the Antibiotics Industry

In foregoing sections of this chapter the importance of patents disclosing specific antibiotic products, for example, tetracycline and chlortetracycline, has been indicated. As of 1956, the 11 principal corporate producers of antibiotics owned over 500 antibiotic patents (exclusive of antibiotics in combination with other drugs). (See table 63.)

[31] Henry Welch, Principles and Practices of Antibiotic Therapy, Medical Encyclopedia, Inc., Blakiston Co., New York; 1954, p. 169. Dr. Welch states at p. 172: "Of 30 strains of staphylococcus, 25 of which were resistant to penicillin, streptomycin, and the broad spectrum antibiotics, all were found to be sensitive to erythromycin."

TABLE 63.—*Antibiotics patents acquired by the United States and 11 principal corporate producers of antibiotics: 1942 to 1956*

Name of patent owner	Total	Penicillin	Streptomycin and dihydrostreptomycin	Broad spectrum				Erythromycin	Other [1]
				T	C	O	Chlor.		
Abbott	10	5	2					1	2
American Cyanamid	60	15	4	9	16				16
American Home Products	29	15	4						10
Bristol Laboratories	50	38	8	4					
Commercial Solvents	48	25	4						19
Lilly	67	60	3				1	3	
Merck	111	68	35						8
Olin Mathieson	40	15	18						7
Parke, Davis	42	6					35		1
Pfizer	40	5	20	1		3			11
Upjohn	20	10	2						8
United States	34	9							25
Total	551	271	100	14	16	3	36	4	107

Abbreviations: T—tetracycline, C—chlortetracycline, O—oxytetracycline, Chlor.—chloramphenicol.

[1] Includes bacitracin, neomycin, tyrothricin, viomycin, polymyxin, actidione, fumagillin, carbomycin, anisomycin, cycloserine, oleandomycin, patulin, thioaurin, acetopyrrothine, netropsin, subtilin, gramacidin, aureotracin, mycosubtilin, actinomycin, prodigiosin, ascosin, endomycin, grisein, circulin, cycloheximide.

Source: Patent Office classification files.

Approximately 50 percent of all patents owned by the 11 principal manufacturers of antibiotics relating to these products concern penicillin or processes for its production. Each of the 11 principal manufacturers of antibiotics owns penicillin patents, though the number of such patents held by the various companies varies widely. Merck owns the greatest number, 68, followed by Lilly with 60, Bristol with 38, American Cyanamid, American Home Products and Olin Mathieson with 15 each, and Upjohn with 10. Each of the remaining companies specified in table 63 own less than 10 patents with penicillin as subject matter.

One example will serve to illustrate the manner in which patenting developed among manufacturers of penicillin. During the early stages of commercial marketing of penicillin, great difficulty was encountered in administration of this drug, since in its natural state penicillin is quickly excreted. Eventually, scientists discovered that penicillin, when reacted with another chemical known as "procaine," remained present and active in the blood stream for much longer periods of time than had been the case with any previously known methods of administration. A dominant patent was obtained in July 1950 by Eli Lilly & Co. on the composition product "Procaine Penicillin and Therapeutic Compositions." Thereafter no procaine penicillin salts could be produced or sold by competitors of Lilly without a license from Lilly. Since Lilly's procaine penicillin patent was issued, 16 additional procaine penicillin patents have been assigned to the pharmaceutical houses listed in table 64.

As indicated in table 63, the streptomycin-dihydrostreptomycin patent situation is similar to that of penicillin from the standpoint of distribution of ownership. Streptomycin patent ownership is somewhat more concentrated, Merck owning 35 and Pfizer 20 out of a total of 100 patents on these two antibiotics. Merck and Pfizer account for a greater portion of total streptomycin-dihydrostreptomycin sales than do any of the other patent owners.

Each of the 11 principal pharmaceutical houses producing antibiotics owns patents relating to penicillin; all of them except Parke, Davis & Co. own patents on either streptomycin or dihydrostreptomycin. A different situation prevails with respect to ownership of patents relating to broad spectrum antibiotics and erythromycin.

A case in point is oxytetracycline, known generally by its trademark Terramycin.[32] Only three patents with this antibiotic as subject matter have been issued, compared with 271 penicillin patents and 100 streptomycin or dihydrostreptomycin patents. All three Terramycin patents are owned by Pfizer. Medicinal Terramycin sales, measured in dollars, were much greater than total medicinal streptomycin and dihydrostreptomycin sales in 1956, and were half as much as medicinal penicillin sales in that year.

TABLE 64.—*Ownership of patents relating to the procaine penicillin, salt and compositions thereof*

Patent No.	Title	Assigned to—	Date of issuance
2,528,174 2,528,175 2,528,176 2,528,177	Procaine salts of biosynthetic penicillin	Lilly	Oct. 31, 1950
2,643,251	Precipitation of fine particle procaine penicillin G	Bristol	June 23, 1953
2,676,961	Procaine penicillin preparation	Physiological Chemical.[1]	Apr. 27, 1954
2,694,665	Procaine penicillin G composition	Upjohn	Nov. 16, 1954
2,712,009 2,712,010	Preparation of habit-modified procaine penicillin	American Home Products.	June 28, 1955
2,725,336	Preparation containing modified procaine penicillin crystals and process for preparing such crystals.	Pfizer	Nov. 29, 1955
2,727,892	Preparation of procaine penicillin	do	Dec. 20, 1955
2,734,845 2,734,846	Aqueous suspension of procaine penicillin and acid salt of antihistamine.	Schenley	Feb. 14, 1956
2,739,098	Procaine penicillin	Merck	Mar. 20, 1956
2,739,962	Production of crystalline procaine penicillin	Commercial Solvents	Mar. 27, 1956
2,749,274	Stable aqueous procaine penicillin suspension	Bristol	June 5, 1956

[1] This patent subsequently assigned to Union Carbide Corp.

Chlortetracycline, commonly known by its trademark, Aureomycin,[33] is manufactured and sold as such by only one pharmaceutical house, American Cyanamid Co. All 16 patents relating to this antibiotic, including a patent on the product itself, are owned by Cyanamid.

[32] Terramycin is the registered trademark of Chas. Pfizer & Co., Inc.
[33] Aureomycin is the registered trademark of Lederle Laboratories Division of American Cyanamid Co.

There are 36 patents, including a product patent, covering Chloromycetin.[34] All except one of these patents are owned by Parke, Davis & Co.

The fourth and most important broad spectrum antibiotic, indeed, the most important of all antibiotics at the present time, if measured in terms of dollar sales, is tetracycline. As of September 1956, 14 patents relating to tetracycline and its production had been issued. The most important, covering the product itself, is owned by Pfizer. Additional patents on processes and on compounds are owned by Cyanamid (9) and Bristol (4). None are owned by Olin Mathieson and Upjohn, which, as heretofore noted, are licensees under the tetracycline product patent.

Erythromycin sales in recent years have ranked along with those of chlortetracycline (Aureomycin), and chloramphenicol (Chloromycetin). Only four patents relating to erythromycin have been issued, three of which, including the product patent, are owned by Lilly. The fourth patent is owned by Abbott Laboratories. Two licenses to manufacture, use, and sell erythromycin have been granted by Lilly, one to Abbott Laboratories, the other to Upjohn.

Patent Licensing in the Antibiotics Industry

In a previous section of this chapter, entitled "Product Patents in the Antibiotics Industry," the licensing of some of the most important antibiotic product patents has been discussed. Particular attention has been given to the licensing of product patents covering streptomycin, dihydrostreptomycin, chloramphenicol (Chloromycetin), chlortetracycline (Aureomycin), oxytetracycline (Terramycin), tetracycline, and erythromycin.

In the present section it is proposed to discuss somewhat more general licensing arrangements in the antibiotics industry, extending to patents covering antibiotic processes, compositions, and improvements thereon, as well as certain additional product patents.

As has been described, the Lilly, Abbott, and Upjohn agreement which commenced during World War II provided for reciprocal licensing under all antibiotics patents obtained from patent applications filed prior to July 18, 1957, relating to information known on cultures existing as of July 18, 1952. Information as to patent ownership submitted to the Federal Trade Commission by these three companies in September 1956, plus data compiled by the Commission through a search of Patent Office classification files subsequent to receipt of information from the companies, indicate that the three companies own a total of at least 97 patents related to antibiotic substances. Of the total, Lilly owns at least 67 of these patents; Up-

[34] Chloromycetin is the registered trademark of Parke, Davis & Co.

john owned about 20: and Abbott at least 10. (See table 63, this chapter, for classification of these patents by product.) Under terms of the agreement, each of the companies is entitled to licenses under patents held by the other two companies.

Apart from its agreement with Abbott and Upjohn, Eli Lilly & Co., Inc., has executed a cross-licensing agreement with Biochemie G. m. b. H., an Austrian company, by terms of which Lilly is exclusive licensee with the right to grant sublicenses under specified Biochemie patents in certain countries, including the United States.[35] These Biochemie patents cover processes for production of phenoxymethyl penicillin and also contain certain product claims. Lilly owns the phenoxymethyl product patent in the United States. This patent was issued to Lilly in 1951. Only one company, Wyeth Laboratories (American Home Products Corp.), has been licensed by Lilly under these phenoxymethyl penicillin patents, so far as is known. Abbott and Upjohn would appear to be entitled to licenses under these patents as a consequence of the Abbott-Upjohn-Lilly cross-licensing agreement, although Lilly and Wyeth are the only companies presently marketing phenoxymethyl penicillin, as such.

A substantial block of antibiotics patents, numbering at least 34, is owned by the United States Government. These patents are the result of research activities by the various Federal agencies. Royalty-free licenses under any or all of these patents may be obtained by any qualified applicant in the United States. One of these patents discloses bacitracin,[36] preparations of which are marketed by several manufacturers of antibiotics. However, this product is primarily useful for nonprescription ointment preparations, and is used only to a limited extent for internal treatment.

Certain of these patents, which disclose processes for the production of penicillin, and which are based upon discoveries made by Dr. Andrew W. Moyer in the early 1940's, are of great importance.[37] Among the inventions covered by these patents is the use of corn-steep liquor as a nutrient medium in the fermentation of penicillin—a discovery which greatly increased yields of penicillin.

Although Dr. Moyer was obligated by the terms of his employment contract with the Department of Agriculture to assign all of his domestic patent rights to the United States Government, various foreign patents corresponding to the United States patents were obtained. Dr. Moyer retained foreign patent rights to his inventions. Commercial Solvents Corp., Merck & Co., and Squibb Division of Olin Mathieson Chemical Corp. negotiated an agreement empowering Commercial Solvents to purchase them from Dr. Moyer. Merck

[35] FTC data request, 1956.
[36] U. S. Patent No. 2,498,165.
[37] U. S. Patents Nos. 2,442,141, 2,443,989, and 2,476,107.

and Squibb each agreed to reimburse Commercial Solvents in an amount equal to one-third of the purchase price, so long as it did not exceed a specified amount, in return for Commercial Solvents' agreement to license Merck and Squibb under the foreign patents after acquiring title to them.[38]

Patents owned by research foundations, such as the Rutgers Research and Endowment Foundation, have been licensed to qualified applicants in return for payment of specified royalties. And there are various instances of domestic licensing arrangements relating to a particular product or process patent between or among two or more manufacturers of antibiotics. These agreements do not involve any features not covered in this discussion, however, and are not regarded as of sufficient importance to warrant consideration of each individual licensing agreement.

Many licenses under antibiotics patents have been obtained as a result of negotiated agreements settling interferences in the Patent Office. An interference is a proceeding instituted in the Patent Office to determine priority of invention where two or more parties claim substantially the same invention. The purpose of the interference is to determine which applicant did, in fact, first make the invention.[39]

Seventy interferences were declared relating to antibiotics patents issued prior to September 1956, to which one or more of the 11 manufacturers of antibiotics listed in table 63 was a party.[40] Fifty of these were settled by negotiated agreements among the parties involving concessions of priority to one of the parties in return for that party's promise to license the other parties under any patent eventually obtained.[41] Table 65 classifies these 50 interference settlement agreements by type of antibiotic.

[38] Agreement dated September 28, 1948, between Commercial Solvents Corp., Merck & Co., and Squibb (now Squibb Division of Olin Mathieson Chemical Corp.), submitted to the Federal Trade Commission in response to FTC data request, 1956.

[39] There are two principal methods of arriving at such a determination: (1) after arguments before an official of the Patent Office known as an interference examiner, and after his consideration of all evidence submitted by the parties in support of their contentions, the interference examiner can make a finding of fact and award the patent claim to the party which he finds to be the prior inventor. If this occurs, the other parties are excluded from practicing the invention after the patent is issued, unless they successfully appeal the interference examiner's decision; (2) the parties placed in the interference can formally concede priority of invention to one of the other parties by filing a written concession with the interference examiner. Normally the price for a concession of priority by one party to an interference is an agreement by the opponent to grant a license at reasonable royalty when and if he obtains a patent on the invention. A similar result is attained where one party to an interference states in writing that he abandons his application, or files a written disclaimer. U. S. Patent Office Rules of Practice, September 1955, Rule 261, et. seq.

[40] Information as to the total number of interferences involving antibiotics patents was obtained from the files of all antibiotics patents issued prior to September 1956 to the 11 pharmaceutical houses listed in table 63. All information in these files relating to interferences was then correlated to eliminate duplication.

[41] Settlement agreements of 50 interference proceedings submitted by the 11 corporate manufacturers listed in table 63 in response to FTC data request, 1956.

TABLE 65.—*Interference settlement agreements classified by type of antibiotic: 1943 to 1956*

Antibiotic	Interferences settled	Patents issued to 11 companies
Penicillin	35	262
Streptomycin	5	100
Dihydrostreptomycin	1	
Tetracycline	1	14
Oxytetracycline	0	3
Chlortetracycline	0	16
Chloramphenicol	0	36
Erythromycin	0	4
Other	8	82
Total	50	517

Thirty-five interferences involving penicillin have been settled by negotiated agreement. Many of these agreements contain provisions similar to those of the dihydrostreptomycin interference settlement agreement, which will be described later in this chapter. At first glance it may appear curious that so many more interferences have been settled involving penicillin than any other antibiotic. This is no doubt due in part to the fact that there are far more issued patents relating to penicillin than any other antibiotic. Table 63 shows that almost 50 percent of all patents owned by the 11 corporations covered in this analysis are penicillin patents. All of these corporations have had applications on file for penicillin patents, which increased the likelihood of conflicting claims to the same penicillin inventions.

An important illustration of licensing in the penicillin field resulting from interference settlement agreements is procaine penicillin. As described in greater detail later in this chapter, five different applicants—Merck, Pfizer, Lilly, Bristol, and Dr. Simon L. Ruskin—owned patent applications on procaine penicillin. After an interference was declared among these applications, and after one party, Dr. Simon L. Ruskin, was eliminated from the interference, Merck, Pfizer, and Bristol conceded priority to Lilly, receiving in return licenses under the patent, which was issued July 18, 1950. Cutter Laboratories also received a license from Lilly following Cutter's concession of priority in another interference proceeding. In addition, Abbott and Upjohn obtained licenses under Lilly's patent, possibly as a result of the comprehensive cross-licensing arrangement among these companies heretofore described. Three companies—Heyden, Baker, and Schenley—obtained licenses following the settlement of patent infringement suits brought by Lilly. Five other companies—Cyanamid, Squibb, Wyeth, Commercial Solvents Corp., and Parke, Davis—have also been licensed under Lilly's procaine penicillin patent.

Only three licenses have been granted under the benzathine penicillin product patent owned by Wyeth. All three licenses were the

result of interference settlement agreements among Wyeth, Pfizer, Bristol, and Lilly.

There have been no interferences relating to oxytetracycline (Terramycin), chlortetracycline (Aureomycin), chloramphenicol (Chloromycetin), and erythromycin because, so far as is known, no conflicting patent applications have been pending regarding these four antibiotics. Tetracycline patent applications have been in two interferences, one of which was settled by cross-licensing and concession of priority, the other of which was dissolved by the patent examiner on his own motion. These two interferences are discussed in a later section of this chapter.

Five interferences involving streptomycin patent applications have been settled by negotiated agreements. All of these are similar in their provisions to the dihydrostreptomycin agreement discussed below. Priority of invention to the product dihydrostreptomycin was the subject of an interference between Merck & Co., Squibb Division of Olin Mathieson Chemical Corp., and Parke, Davis & Co. Following declaration of this interference, the three parties agreed on March 22, 1948, to furnish to each other all evidence relevant to the issue of priority of invention, rather than continue the proceeding before the Patent Office interference examiner.[41a] The agreement provided that if, after examination of all the evidence by their attorneys, they were unable to agree which party was, in fact, the first inventor, then a stipulated statement of facts would be presented to the Patent Office for decision solely on the issue of priority of invention. In the event controversies arose among the three relating to other issues than priority of invention, arbitration procedures were agreed upon.

Following decision of the question which party first invented dihydrostreptomycin, the losing parties were to concede priority in the Patent Office, receiving licenses in return to make, use, and sell dihydrostreptomycin from the ultimately successful patentee. The licensees agreed to pay to the patentee a royalty based upon a percentage of their net sales of dihydrostreptomycin. The reason for special attention to this dihydrostreptomycin interference settlement is, as stated above, that it is similar in its provisions to many of the 50 interference settlement agreements submitted to the Federal Trade Commission by the corporations replying to the 1956 FTC data request.

The 50 interferences settled by negotiated agreements along the lines of the dihydrostreptomycin agreement described above constitute 71 percent of all interferences declared prior to September 1956 involving antibiotic patent applications owned by 11 leading corporate manufacturers of antibiotics. Considerations of time and expense are

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[41a] Agreement dated March 22, 1948, submitted by Merck & Co., to the Federal Trade Commission in response to FTC data request, 1956.

frequently important factors in the settlement of interferences. According to one authority, "cases continue to arise where by reason of one or more interferences and related court proceedings—a patent issues long after its filing date and even after the patent would have expired if issued in normal course." [42]

Before rejecting a rival's offer to negotiate an interference settlement, a patent applicant is likely to consider the probability that a rival who foresees defeat in an interference will, rather than be excluded entirely from practicing the invention, attempt to convince the examiner that the invention itself is unpatentable. In Patent Office terminology, the opponent may move to dissolve the interference on grounds of the unpatentability of the invention. In a survey reported by Mr. P. J. Federico, examiner in chief of the Patent Office, motions to dissolve on grounds of unpatentability were made in 31 out of 100 interferences surveyed. Mr. Federico states, "These motions were successful in whole or in part in 42 percent of the interferences in which they were brought." [43]

Factors of time and expense, and the possibility of motions to dissolve on grounds of unpatentability, have doubtless been of some influence in motivating settlement agreements of some of the antibiotic interferences.

Significant Patent Litigation

Procaine penicillin

Litigation over patent rights relating to procaine penicillin has been characterized by two distinct aspects: (1) a conflict arising out of claims by five separate parties to patent rights covering this product, in which the principal issue was priority of invention among the five applicants; (2) infringement suits brought to prevent unlicensed manufacturers from producing, using, and selling procaine penicillin. The importance of patent rights to this product becomes apparent when it is realized that procaine penicillin has represented about two-thirds of total penicillin production since 1950.

The initial patent on this product, United States Patent 2,515,898, was issued to Eli Lilly & Co., Inc., on July 18, 1950. Prior to this date Lilly's patent application had been involved in Interference No. 83786, declared March 23, 1949, with four other applications relating to procaine penicillin. These were owned by: Chas. Pfizer & Co., Inc.;

[42] George E. Frost, "The Patent System in the Modern Economy," Study No. 2, Subcommittee on Patents, Trademarks, and Copyrights of the Committee on the Judiciary, U. S. Senate, 84th Cong., 2d sess., pp. 66–67.

[43] P. J. Federico, "Opposition and Revocation Proceedings in Patent Cases," Study No. 4, the Subcommittee on Patents, Trademarks, and Copyrights, U. S. Senate Committee on the Judiciary, Government Printing Office, 1957, p. 14.

Merck & Co., Inc.; Bristol Laboratories, Inc.; and Dr. Simon L. Ruskin, a New York physician.

As a result of motions by Bristol, Pfizer, and Lilly, Dr. Ruskin was eliminated from this interference late in 1949. However, on October 31, 1949, Dr. Ruskin petitioned the Commissioner of Patents asking to be restored to the interference. Following a hearing on March 23, 1950, Dr. Ruskin was finally eliminated from this interference.

Prior to this date, Lilly, Bristol, and Merck had agreed to settle among themselves their own conflicting claims to inventorship of procaine penicillin. The provisions of this agreement were to become effective "when and if Ruskin is finally eliminated from said interference by any means." [44]

In suceeding paragraphs of this agreement, Merck and Bristol each agreed to assign its domestic patent application [45] covering procaine penicillin, and "all corresponding foreign patents and pending patent applications" to Lilly.[46] Earlier, in 1948, Pfizer and Lilly had executed a similar agreement, though this earlier agreement contained royalty-sharing provisions not present in the Lilly-Merck-Bristol agreement of March 22, 1950, nor did it make any reference to Dr. Ruskin's application. The Lilly-Pfizer agreement was not to become effective until settlement was reached between Lilly, Merck, and Bristol, however.[47]

Attorneys for Merck, Bristol, and Lilly were to decide which patent applications were to be further prosecuted by Lilly. All parties to the March 1950 agreement, and in addition Pfizer, were to be licensed by Lilly under specified foreign patents and under future domestic and foreign patents resulting from patent applications subject to the agreement.

After obtaining the procaine penicillin patent in July 1950, Lilly instituted suit against three unlicensed competitors which were making and selling procaine penicillin: Schenley Laboratories, Inc., Heyden Chemical Corp., and J. T. Baker Chemical Co. On May 14, 1953, Lilly obtained a judgment against Schenley in the United States District Court for the Southern District of Indiana, the court holding Lilly's patent to be valid and infringed.[48] On January 14, 1954, Lilly's suit against Heyden was settled by agreement, Heyden receiving a license in return for payment of a specified royalty.[49]

On February 26, 1954, a settlement was reached between Lilly and Schenley. Schenley was granted a license in consideration of Schen-

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[44] FTC data request, 1956.

[45] Merck Application Serial No. 791,158, filed December 11, 1947; Bristol Application Serial No. 782,466, filed October 27, 1947.

[46] FTC data request, 1956.

[47] Ibid.

[48] *Eli Lilly & Co.* v. *Schenley Laboratories Inc.*, 112 F. Supp. 296 (S. D. Ind. 1953).

[49] FTC data request, 1956.

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ley's agreement not to appeal from the District Court decision, and in return for payment of a specified percentage royalty by Schenley to Lilly.[50]

The suit against J. T. Baker Chemical Corp. was settled by agreement dated June 30, 1956, on a basis similar to the earlier Lilly-Heyden settlement described above.[51]

Meanwhile, Dr. Ruskin, following his final elimination from the interference early in 1950, had continued his efforts to obtain a patent on procaine penicillin by ex parte prosecution of his application before the Patent Office. On September 27, 1950, Eli Lilly & Co. petitioned the Commissioner of Patents to institute public use proceedings to bar Dr. Ruskin from receiving a patent on procaine penicillin. It was claimed by Lilly that public use and public knowledge of procaine penicillin in 1943 and 1944 barred Dr. Ruskin's claims to procaine penicillin (based upon his 1945 patent application). After 4 years of testimony and arguments, it was decided by the Patent Office early in 1954 that no public use proceedings should be instituted against Dr. Ruskin.

On April 27, 1954, United States Patent 2,676,961, "Procaine-Penicillin Preparation," containing the claim "procaine salt of penicillin" was issued to Dr. Ruskin. On the same day Eli Lilly & Co. filed a civil action in the United States District Court for the Southern District of New York asking that Dr. Ruskin's patent be declared "wholly invalid and void in law," because it lacked novelty, lacked invention, had been in public use, and had been "granted by the United States Patent Office in reliance on false and fraudulent representations made to the Patent Office by Ruskin and other persons acting in his behalf." [52]

Each of these allegations was denied by Dr. Ruskin in his answer.[53]

Dr. Ruskin filed suit against Lilly in the United States District Court for the Southern District of Indiana on April 27, 1954, asking the court to declare Lilly's procaine penicillin patent invalid, and requesting that Lilly be enjoined from future infringement of Dr. Ruskin's procaine penicillin patent.[54]

Another action against Lilly was filed by Dr. Ruskin on April 27, 1954, this one in the United States District Court for the Southern District of New York.[55] In his complaint, Dr. Ruskin alleged that

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[50] Ibid.

[51] Ibid.

[52] *Eli Lilly & Co.* v. *Simon L. Ruskin et al.*, Civil Action No. 92–367, U. S. District Court for the Southern District of New York, filed April 27, 1954.

[53] *Eli Lilly & Co.* v. *Simon L. Ruskin et al.*, Civil Action No. 92–367, U. S. District Court for the Southern District of New York, answer filed May 3, 1954.

[54] *Physiological Chemical Company, Inc.* v. *Eli Lilly & Co.*, U. S. District Court for the Southern District of Indiana, Indianapolis Division, No. 3714 Civil, filed April 27, 1954.

[55] *Simon L. Ruskin and Physiological Chemicals Co., Inc.* v. *Eli Lilly & Co.*, Civil Action No. 92–374, U. S. District Court for the Southern District of New York.

the attempted public use proceeding by Lilly, which lasted from 1950 to 1954, "was instituted by defendant maliciously and without probable cause and for the calculated and intended purpose of delaying or otherwise improperly obstructing plaintiff's efforts to obtain patent protection for said procaine salt of penicillin and for the deliberate purpose of causing damage to plaintiffs."[56] These allegations were denied by Lilly in its answer to the complaint.[57]

On September 30, 1954, as a result of a motion by Dr. Ruskin, Chas. Pfizer & Co., Inc., was added as a defendant in the New York action against Lilly.

In his amended complaint, Dr. Ruskin alleged that defendants had conspired "* * * to file a petition in the United States Patent Office for the institution of a public use proceeding alleging a public use more than 1 year prior to the original filing of plaintiff's application, although defendants knew at the time of the filing of such proceedings and continuously thereafter that there was no basis in fact for its instituting such a proceeding."[58]

Each of these allegations were denied by Pfizer in its answer to Dr. Ruskin's amended complaint.[59]

On February 18, 1957, after 3 years of court litigation, Dr. Ruskin assigned his procaine penicillin patent to the Union Carbide Corp. Thereafter Union Carbide Corp. initiated negotiations with Lilly looking toward a settlement of the Indiana infringement action, and in May 1957 the suit was settled.

On May 22, 1957, Civil Action No. 92–374, Dr. Ruskin's action against Lilly and Pfizer, then pending in the United States District Court for the Southern District of New York, was dismissed with prejudice upon consent of all parties to the action.[60]

Tetracycline

The tetracycline patent was issued to Chas. Pfizer & Co., Inc., on January 11, 1955, and on the same day this company filed infringement suits to prevent Bristol Laboratories, Inc., Olin Mathieson Chemical Corp., and The Upjohn Co. from making, using, or selling tetracycline. Thereafter, on January 25, 1955, each of these three unlicensed sellers filed suit for a declaratory judgment that the tetracycline patent be held invalid.

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[56] Ibid.

[57] Ibid.

[58] *Simon L. Ruskin and Physiological Chemicals Co., Inc.* v. *Eli Lilly & Co. and Chas. Pfizer & Co.*, Civil Action No. 92–374, U. S. District Court for the Southern District of New York.

[59] Ibid.

[60] On June 3, 1954, Lilly's infringement suit against Dr. Ruskin had been dismissed without prejudice upon consent of the parties thereto, presumably because the same issues were to be litigated in Dr. Ruskin's action against Lilly and Pfizer which at that time had been pending in New York and which was dismissed on May 22, 1957, as indicated above.

Like procaine penicillin, in terms of sales tetracycline is an important antibiotic. Approximately $73 million worth of tetracycline was sold at the manufacturer's level in 1956 representing almost 25 percent of total sales of all antibiotics in that year; and tetracycline sales comprised almost 50 percent of total broad spectrum antibiotics sold for therapeutic purposes in 1956.

The importance attributed to the tetracycline patent by two leading members of the antibiotics industry, Pfizer and American Cyanamid Co., may be illustrated by quotation of statements made by representatives of these companies during the course of interference proceeding before the Patent Office. Nine days after Interference No. 86,861 was declared involving patent applications owned by Pfizer, Cyanamid, and Bristol, Pfizer filed formal notice in the Patent Office that it would "oppose all motions for extension of time in these proceedings * * * the undersigned attorneys * * * desire to give advance notice of their inability to extend the customary courtesies to suit the convenience of opposing counsel or of the parties they represent."[61] Reasons given by Pfizer's attorneys for this step were that "the subject matter of this interference is of such immediate and tremendous commercial importance that every delay in the issuance of a patent therefore causes most substantial and irreparable injury to the party entitled to receive such patent."

During the course of this interference, Cyanamid argued:

> The development of channels of distribution, the enlargement of manufacturing facilities, and the expenditure of millions of dollars in research and development will be adversely affected until inventorship of the subject matter has been determined.[62]

Pfizer filed a five-page affidavit, signed by Vice President John L. Davenport, stating in part:[63]

> It is of the utmost importance that the present interference be resolved with the greatest possible speed because of the extreme commercial importance of the subject matter involved * * *. Pfizer sales promotion, the expansion of its productive facilities and employment of additional labor for manufacture of the new antibiotic have been and will be seriously impeded by every delay encountered in disposition of the interference.
>
> Most importantly * * * Cyanamid has conceded priority to Pfizer with respect to the product tetracycline and the process of manufacturing it by hydrogenation of chlortetracycline * * * the agreement between Cyanamid and Pfizer * * * calls for the payment of royalty * * * from the day that the patent issues * * * should the patent issue to Pfizer these royalties, based on the estimated current average volume, of Cyanamid's sales, would be in excess of fifty thousand dollars ($50,000) per month. Thus, Pfizer is losing more than sixteen hundred dollars

[61] U. S. Patent Office Interference File No. 86,861, Paper No. 2, March 10, 1954.
[62] U. S. Patent Office Interference File No. 86,861, Paper No. 10, March 30, 1954.
[63] U. S. Patent Office Interference File No. 86,861, Paper No. 28.

($1,600) for each day delay in the issuance of the patent to Conover who is believed to be the true inventor.

Furthermore, he fears that such delay may encourage others to undertake the manufacture and marketing of the new antibiotic in violation of the putative patent rights of Pfizer, thereby causing it further irreparable damage.

On July 19, 1954, Cyanamid stated:[64]

Grave injury to the commercial position of the other applicants with respect to the product in issue will occur if this proceeding is delayed by the extension of time requested.

In a subsequent paper with respect to Bristol's argument to the examiner, Cyanamid explained to the Patent Office that it "would rather pay royalties to a bona fide patentee than see the pharmaceutical business in which it has a major interest ruined by irresponsible price cutting." Its attorneys stated:[65]

Worst of all, as the interference is delayed, the Bristol production and sales will undoubtedly increase in volume, and the selling price on the product will be lowered so that at the termination of the interference the profits from which research funds come, will have been reduced to nothing. When the interference is terminated, if Heinemann et al. are allowed to drag their feet and delay the proceedings, the tetracycline business may resemble the present penicillin situation, wherein some of the larger manufacturers have been forced to discontinue the manufacture of penicillin, and the others are making little, if any, profit. This situation is inimical to the best interests of the country as a whole because under the capitalistic system under which American business operates, a profit must be made to pay for continuing research to develop new and better antibiotics.

Tetracycline was developed in 1952, more than 3 years after the other 3 broad spectrum antibiotics, oxytetracycline (Terramycin), chlortetracycline (Aureomycin), and chloramphenicol (Chloromycetin). After its appearance on the market, tetracycline made swift and deep inroads into sales of the three earlier marketed broad spectrum antibiotics.

Unlike procaine penicillin, tetracycline was not being produced by numerous manufacturers at the time of the issuance of the product patent. As has been indicated there were 14 producers of procaine penicillin a patent on that product issued, and all were eventually licensed to produce it. There were 3 producers of tetracyline when Pfizer obtained the patent on this product. One, Cyanamid, was licensed by Pfizer as a result of a cross-licensing agreement settling an interference in the Patent Office. The other, Bristol, was licensed in the course of the legal disputes set out below. Squibb and Upjohn were selling the product after purchasing it from Bristol and they received licenses from Pfizer to continue to do so.

[64] U. S. Patent Office Interference File No. 86,861, Paper No. 29, July 19, 1954.
[65] U. S. Patent Office Interference File No. 86,861, Paper No. 36, August 13, 1954.

The origin of tetracycline.—Terramycin and Aureomycin have closely similar medical activity and almost identical empirical chemical formulae.[66]

They have been revealed to have chemical structure *A* (see chart 9) in common. The only difference in the chemical structures of Aureomycin and Terramycin has been shown to be the presence of a chlorine group at position X of the Aureomycin molecule (structure *B*, chart 9), which Terramycin lacks; and the presence of a hydroxyl group at position *Y* on the Terramycin molecule (structure *C*, chart 9), which Aureomycin lacks.

Lloyd H. Conover conceived the idea of removing the chlorine group present on the Aureomycin molecule by the chemical technique of hydrogenating Aureomycin in the presence of a metal catalyst, such as palladium.[67]

On June 27, 1952, Conover succeeded in performing this experiment and produced a chemical compound having a chemical structure identical to that of Aureomycin without a chlorine group *X*, and to Terramycin without hydroxyl group *Y*.[68] The word "tetracycline" was coined in the Pfizer organization for this antibiotic.[69]

On October 23, 1952, Conover, through Pfizer's patent agent, applied for a patent in the United States Patent Office.

On July 23, 1953, this application for a tetracycline patent was rejected by the patent examiner on the basis that the nature of the product, tetracycline, had been disclosed in previously granted patents on Terramycin and Aureomycin.[70]

The first tetracycline interference.—Following the rejection, Pfizer redrafted the claims of the original application and substituted a new application on October 9, 1953 as a continuation-in-part of the earlier application.[71]

Earlier, on March 16, 1953, inventors of Lederle Laboratories Division of the American Cyanamid Co., Boothe and Morton by name, had filed a patent application in which they claimed invention of the same product and the same process claimed by Conover for Pfizer. On December 28, 1953, Interference No. 86,799 was instituted for the purpose of determining which of the parties, Cyanamid or Pfizer, was entitled to a patent on the product tetracycline and the process of producing it by catalytic hydrogenation of Aureomycin.[72]

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[66] Deposition of Lloyd H. Conover on Feb. 15, 1955, Pfizer chemist, in Civil Action No. 98–221, U. S. District Court for the Southern District of New York, p. 49.

[67] U. S. Patent 2,699,054, "Tetracycline."

[68] Deposition of Lloyd H. Conover, Feb. 17, 1955, *supra*, p. 188.

[69] Deposition of Francis X. Murphy, Sept. 21, 1955, in Civil Action No. 98–221, U. S. District Court, Southern District of New York, p. 104.

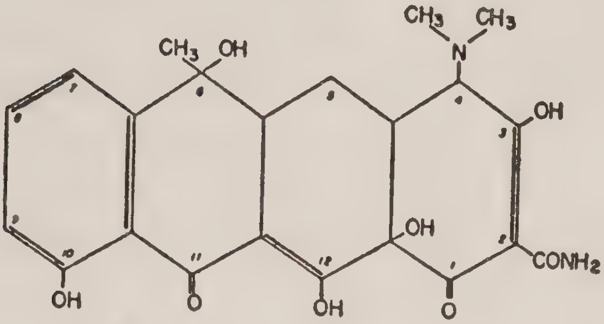
[70] U. S. Patent File S. N. 319,543. Office action dated July 23, 1953.

[71] U. S. Patent File No. 2,699,054, Paper No. 1.

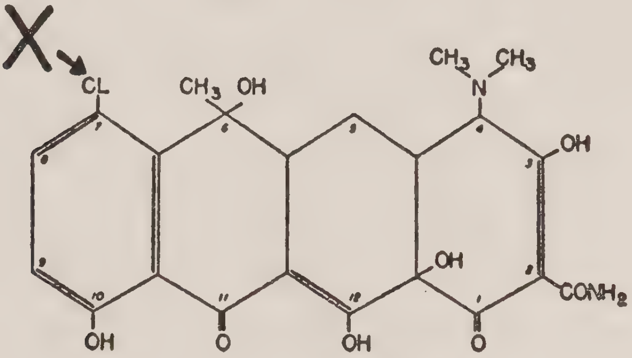
[72] U. S. Patent File No. 2,699,054, Paper No. 6.

CHEMICAL STRUCTURE OF TETRACYCLINE CHLORTETRACYCLINE, AND OXYTETRACYCLINE.

A TETRACYCLINE



B CHLORTETRACYCLINE (AUREOMYCIN)



C OXYTETRACYCLINE (TERRAMYCIN)

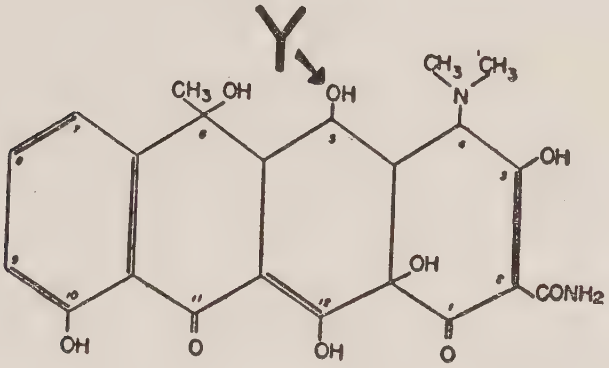


CHART 9.

Source: Henry F. Dowling, Tetracycline, Medical Encyclopedia, Inc., New York, 1955, p. 14.

Two weeks later, on January 11, 1954, Pfizer and Cyanamid entered into an agreement looking toward the amicable settlement of this interference. By the terms of the agreement, Cyanamid licensed Pfizer to produce chlortetracycline (Aureomycin) "for use solely in the manufacture of Tetracycline by means of the deschlorination of chlortetracycline so manufactured." [73] For some time prior to this, Pfizer had considered the only "drawback" about Conover's discovery to be the fact that somehow a license to make chlortetracyline (Aureomycin) under Cyanamid's Aureomycin patent would have to be obtained from Cyanamid.[74] The "drawback" was thus successfully remedied.

[73] Agreement dated Jan. 11, 1954, between Chas. Pfizer & Co., Inc., and American Cyanamid Co., p. 9, FTC data request, 1956.

[74] Deposition of Francis X. Murphy, *supra*, Sept. 20, 1955, pp. 56–57.

The agreement provided for cross-licensing of all patents covering tetracycline and its preparation by this process regardless of which party secured the patent.

Cyanamid also agreed to furnish Pfizer its know-how (which was to include yields of product obtained) and to make available the cultures it then used for the production of chlortetracycline.

The agreement assured Cyanamid the right to manufacture and sell tetracycline and of royalty income from Pfizer sales of tetracycline even if Pfizer were eventually to be granted a patent on tetracycline. Under the license granted by Cyanamid to Pfizer to manufacture chlortetracycline, Pfizer agreed to pay as royalty certain percentage of its domestic net sales of tetracycline to Cyanamid. Were Cyanamid to get the tetracycline patent, Pfizer would be obligated to pay an additional percentage of its net sales of tetracycline. Conversely, if Pfizer got the patent, Cyanamid agreed to pay to Pfizer a percentage royalty on Cyanamid's net sales of tetracycline; at the same time, however, Pfizer would be required to pay Cyanamid a certain percentage on Pfizer's net sales of tetracycline. In this event, under the integrated Pfizer-Cyanamid agreement, no appreciable net amount of royalty would be payable by one to the other so long as net sales of tetracycline by the two companies proceeded at about the same level. Cyanamid was assured, however, of a specified minimum royalty during the years 1954–58.

The parties agreed also to exchange "a full showing of the evidence determinative of priority" of invention of tetracycline with the purpose of reaching agreement as to which party could establish the earlier date of invention. In the event the parties were unable to agree on the question of priority, "then the said question of priority shall be submitted to the United States Patent Office on a record which, so far as possible, shall be stipulated, with the decision of the Board of Patent Interferences being accepted by the parties hereto as final and binding upon them without recourse to appeal."

Cyanamid conceded priority to Pfizer early in February 1954, which resulted in termination of the interference.[75]

The tetracycline "salt" interference. Subsequent to the settlement of Interference No. 86,799, it developed that Bristol Laboratories, Inc., had pending an application for a patent on tetracycline hydrochloride, a chemical salt of tetracycline.

There was also pending in the Patent Office a tetracycline application filed in the name of P. P. Minieri, an employee of Heyden Chemical Corp. On November 30, 1953, Cyanamid purchased the Antibiotic Division of Heyden Chemical Corp., including the aforementioned tetracycline application. Although belonging to Cyanamid

[75] Deposition of Francis X. Murphy, *supra*, Sept. 22, 1955, p. 198.

at the time when the first tetracycline interference between Cyanamid and Pfizer had been declared, the Minieri application had not been placed in the first interference, No. 86,799.

On March 2, 1954, the Patent Office announced that an interference was found to exist between the Pfizer (Conover) application and these two applications.[76] The subject matter of this second interference, tetracycline hydrochloride, has the same chemical and medical actions and uses as tetracycline, and is administered in the same dosages as tetracycline.[77]

On October 14, 1954, the patent examiner announced that tetracycline hydrochloride was unpatentable.[78]

The Examiner's reasoning is set out below: [79]

> At this point the examiner's motion to dissolve will be taken up, since it has a direct bearing on Motion IX and on Motions I and VI. The interference count (tetracycline hydrochloride) is unpatentable over the disclosures of Duggar U. S. 2,482,055, Sept. 13, 1949 (Aureomycin), and Niedercorn U. S. 2,609,329, Sept. 2, 1952 (process patent on the production of Aureomycin), and the interference is dissolved. Duggar and Niedercorn each produce an antibiotic, disclosed as "aureomycin" by a fermentation process employing *Streptomyces aureofaciens* and mutants thereof. The antibiotic is identified as an antibiotic by assay against bacteria. It appears from the disclosure of Minieri et al. (a party to this interference in an application available to all the parties) that tetracycline is *also* produced in such a fermentation process and that larger proportions thereof are produced when the amount of chloride in the fermentation medium is low (see p. 1, lines 5 to 20 and lines 24 to 28, and pp. 12, 16, 17, 18, and 19 of Minieri et al. S. N. 382,637). Minieri et al. clearly and specifically disclose that the microorganism used to prepare *tetracycline* belongs to the Duggar et al. U. S. 2,482,055 species and that "the characteristics are identical with those exhibited by a known culture of *S. aureofaciens*." While neither Duggar or Niedercorn may have realized that tetracycline was in fact produced, they did appreciate, and disclose, that the product was an antibiotic. No invention is involved in the identification of the tetracycline and its hydrochloride inherently produced by the reference process. (See Coe 1943 C. C. 55.) It has long been held that a purer form of an old product is not inventive and the [apparent] mixture of the prior art meets the count. (See *Parke, Davis v. Mulford*, 189 F. 95, and *In re Kelrich*, 96 USPQ 411.)

Further, the patent examiner ruled that the fermentation process for production of tetracycline, claimed by both Cyanamid and Bristol, was unpatentable because "The recovery of an additional antibiotic [tetracycline] from the broth does not confer patentable novelty on the fermentation process which evidently produced the antibiotics [chlortetracycline and tetracycline] concomitantly." [80]

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[76] U. S. Patent Office Interference File No. 86,861, declared March 2, 1954, Paper No. 1.

[77] New and Non-official Remedies, 1956, Philadelphia, Pa.: J. B. Lippincott Co., 1956, p. 143.

[78] U. S. Patent Office Interference File No. 86,861, Paper No. 44, p. 13.

[79] See appendix IV, exhibit 2, for text of the examiner's rejection of Pfizer's patent application claims to tetracycline.

[80] U. S. Patent Office Interference File No. 86,861, Paper No. 44, p. 10.

On November 24, 1954, the parties individually were informed that the product tetracycline could not be patented: "All the product claims, 1 to 6, are rejected as being unpatentable over each of Duggar and Niedercorn for the reasons set forth * * * in Interference No. 86,861." [81]

Thereafter on January 5, 1955, American Cyanamid Co. formally canceled all product claims to tetracycline contained in its application.[82]

Cyanamid's license to Bristol to make tetracycline.—As early as April 1954, Bristol had commenced to make and sell tetracycline. On September 27, 1954, Cyanamid filed suit, alleging that in manufacturing tetracycline, Bristol [83]—

> * * * has been and still is infringing said Letters Patent No. 2,482,055 * * * by making and selling an antibiotic composition containing material disclosed and claimed in said Letters Patent 2,482,055, and, in manufacturing its said antibiotic composition, by making said material and using processes and methods disclosed and claimed in said Letters Patent No. 2,482,055 * * * .

The patent sued upon was Cyanamid's Aureomycin patent. Bristol, however, was making and selling tetracycline. As noted above, the patent examiner dissolved the "salt" interference in October 1954 because of inherent production of tetracycline along with Aureomycin in Cyanamid's Patent No. 2,482,055.

Cyanamid's infringement suit against Bristol was settled by agreement on January 13, 1955.[84] Under this agreement, Bristol was licensed to make, use, and sell "a therapeutically active substance * * * containing tetracycline (as hereinafter defined) * * * and not more than six percent (6%) of chlortetracycline (as hereinafter defined)." [85] Bristol agreed to pay Cyanamid a percentage royalty on the net sales value of all tetracycline products sold by Bristol.

On February 25, 1955, Bristol formally withdrew its patent application on tetracycline, which was still pending before the Patent Office, stating that "all product claims of the character sought in this application are unpatentable. * * * Accordingly, applicants expressly abandoned this application." [86]

Issuance of the tetracycline product patent to Pfizer.—Unlike Cyanamid and Bristol, Chas. Pfizer & Co., Inc., did not accept the patent examiner's rejection as final but continued to prosecute its applica-

[81] U. S. Patent No. 2,699,054, File Paper No. 10. See appendix IV, exhibit 2.

[82] U. S. Patent Office Patent File No. 2,734,018, Record File, Paper Nos. 16 and 17. No. 16 is dated November 24, 1954. No. 17 is dated December 6, 1954.

[83] *American Cyanamid Co.* v. *Bristol Laboratories, Inc.*, Docket 5402, U. S. District Court, N. D. N. Y., Sept. 29, 1954.

[84] FTC data request, 1956.

[85] Ibid.

[86] U. S. Patent Office Patent Application File S. N. 388,048, Paper No. 19, March 1, 1955.

tion, by the submission of additional affidavits of Pfizer scientists to meet the deficiencies indicated by the patent examiner. On January 11, 1955, U. S. Patent 2,699,054, "Tetracycline," was issued to Lloyd H. Conover and assigned by him to Pfizer.

The tetracycline patent litigation.—On the day the patent was issued, three separate actions for infringement of the tetracycline patent were filed by Pfizer in the United States District Court for the Northern District of Georgia, naming Bristol Laboratories, Inc., The Upjohn Co., and Olin Mathieson Chemical Corp. as defendants.[87]

On January 25, 1955 each of the three defendants in the Georgia actions filed an action in the United States District Court for the Southern District of New York, requesting a declaratory judgment "that neither Bristol, through its own activities, nor Squibb [Squibb is a division of Olin Mathieson Chemical Corp.], nor Upjohn, through their dealings in tetracycline and products comprising tetracycline, has infringed or is infringing any valid claim of Patent 2,699,054, or any other patent owned by Pfizer." [88]

One issue was common to all six of these legal actions: the validity of tetracycline product claims in U. S. Patent 2,699,054. There was no question that Bristol was making and selling tetracycline; nor was there any question that Olin Mathieson and Upjohn were buying tetracycline from Bristol and reselling it under their own trademarks and labels.

On March 17, 1955, the judge in the United States District Court for the Northern District of Georgia, on motion of the defendants, ordered the three cases filed in that district transferred to the Southern District of New York.[89] Pfizer's appeal of this order to the United States Court of Appeals, Fifth Circuit, was denied September 16, 1955.[90]

Pfizer's appeal of this order to the United States Court of Appeals, Fifth Circuit, was denied September 16, 1955.[90]

Meanwhile, on April 15, 1955, Pfizer filed answers and counterclaims in the three declaratory judgment actions. In its counterclaims,

[87] *Chas. Pfizer & Co., Inc.* v. *Olin Mathieson Chemical Corp.; Chas Pfizer & Co., Inc.* v. *The Upjohn Co.; Chas Pfizer & Co. Inc.* v. *Bristol Laboratories, Inc.*, Civil Actions Nos. 5082, 5083, 5084, U. S. District Court for the Northern District of Georgia, Atlanta Division, filed January 11, 1955.

[88] *Bristol Laboratories, Inc.* v. *Chas. Pfizer & Co., Inc.; The Upjohn Co.* v. *Chas. Pfizer & Co., Inc.; Olin Mathieson Chemical Corp.* v. *Chas. Pfizer & Co., Inc.*, Civil Actions Nos. 98–221, 98–222, 98–223, U. S. District Court for the Southern District of New York, filed January 25, 1955.

[89] *Chas. Pfizer & Co., Inc.* v. *Olin Mathieson Chemical Corp.; Chas. Pfizer & Co.* v. *The Upjohn Co.; Chas. Pfizer & Co.* v. *Bristol Laboratories, Inc.*, 131 F. Supp. 21 (N. D. Ga. 1955).

[90] *Chas. Pfizer & Co.*, v. *Olin Mathieson Chemical Corp.; Chas. Pfizer & Co.* v. *The Upjohn Co.; Chas. Pfizer & Co.* v. *Bristol Laboratories, Inc.*, 225 F. 2d 718 (C. A. 5, 1955).

Pfizer prayed for injunctions against further infringement of the tetracycline patent and sought damages for infringement and treble damage for the "willful and wanton nature of plaintiff's conduct," as follows:

The Upjohn Co., $10 million and $30 million treble damages; Bristol Laboratories, $5 million and $15 million treble damages; Olin Mathieson, $2 million and $6 million treble damages.[91]

In their replies to Pfizer's counterclaims, the three plaintiffs attacked the validity of the tetracycline product claims of the patent on the grounds of no invention, prior use, and misrepresentation to the Patent Office.

The litigation continued through the summer and fall of 1955. Numerous depositions were taken during this period by defendants. In July 1955 a "tally for Bristol Laboratories in the tetracycline dispute with Charles Pfizer & Co." was noted by Chemical Week magazine.[92] Two Bristol inventors, Joseph Lein and Alexander Gourevitch, had been issued Patent No. 2,712,517 on a direct-fermentation process for making tetracycline. This direct process was described by Mr. Schwarz, president of Bristol, as "greatly increasing the yield [of tetracycline] over other known fermentation processes." [93] Some observers predicted that this might lead to settlement of the tetracycline litigation by a series of cross-licensing agreements.[94] In March 1956, the six tetracycline lawsuits were settled out of court by a series of cross-licensing and licensing agreements.

The tetracycline settlement agreements.—Three separate agreements were executed on March 28, 1956, settling the six tetracycline lawsuits. Pfizer was a party to each of these agreements; Bristol, Olin Mathieson and Upjohn each was a party to only one of the agreements. Only the Pfizer-Bristol agreement can properly be called a "cross-licensing" agreement. The Pfizer-Olin Mathieson agreement and the Pfizer-Upjohn agreement are, in reality, merely licenses granted by Pfizer to Olin Mathieson and Upjohn to sell the product tetracycline. The agreements with Olin Mathieson and Upjohn are identical except for signatures and names, and will therefore be discussed together. Since the Pfizer-Bristol agreement differs both in substance and in detail from the licenses between Pfizer and Olin Mathieson and Upjohn, respectively, it will be discussed separately.

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[91] *Bristol Laboratories, Inc.* v. *Chas. Pfizer & Co., Inc., The Upjohn Co.* v. *Chas. Pfizer & Co., Inc.; Olin Mathieson Chemical Corp.* v. *Chas. Pfizer & Co., Inc.,* Civil Actions Nos. 98–221, 98–222, and 98–223, "Answer and Counterclaim," filed April 15, 1955.

[92] Chemical Week, vol. 77, July 16, 1955, p. 15.

[93] Ibid.

[94] Ibid.

The Pfizer-Bristol agreement: The most important provision of this agreement is article II, "Grant of Licenses and Right to Sublicense." It reads as follows:

> Each party hereby grants the other, its subsidiaries and affiliates, a nonexclusive right and license under the licensed patents [95] of the grantor, its subsidiaries and affiliates, to ferment or otherwise manufacture, make, compound, use and sell licensed products, with the right to grant sublicenses only as hereinafter set forth; it being understood that the license to ferment or otherwise manufacture tetracycline outside the United States may be exercised only through the sublicenses provided for in paragraph 1 of this article.[96]

Pursuant to the agreement, Pfizer licensed Bristol under all of the product claims of U. S. Patent No. 2,699,054, "Tetracycline," "and all independent composition of matter claims included in patents now issued or hereafter issuing in other countries except Australia and Great Britain, to Pfizer * * * corresponding in substance to the composition of matter claims of U. S. Patent No. 2,699,054 * * *." Bristol was also licensed under all the claims of a designated Cuban patent and under four claims of a certain South African patent.

It was agreed that each party would notify the other, in writing, of all patents covering—

(*a*) Tetracycline;

(*b*) The production of tetracycline by fermentation or otherwise (including the use of cultures, organisms, media, or any ingredient thereof, or materials for such purpose, and the recovery or purification of tetracycline so produced);

(*c*) Compositions containing tetracycline or the production of such compositions * * *; or

(*d*) The use or administration of tetracycline or of such compositions.

Each party granted the other an option to take a license under any or all patents owned by each other relating to categories (*a*), (*b*), (*c*), or (*d*) above. Provision was made for sublicensing under all of the licensed patents in all foreign countries where one or the other of the parties had an obligation to an existing licensee.

Each party agreed to pay to the other, as royalty, a specified percentage of the "net sales price" of tetracycline sold while any licenses resulting from the agreement were in effect. Because of Pfizer's product patent, this meant that Bristol would be required to pay Pfizer a specified percentage of Bristol's net sales of tetracycline. Pfizer would be obligated to pay Bristol a specified percentage of Pfizer's net sales

[95] In the agreement, "Licensed Patents" is defined. The term is discussed in detail in the following pages.

[96] Agreement dated March 28, 1956, between Chas. Pfizer & Co., Inc., and Bristol Laboratories, Inc., submitted to the Federal Trade Commission in response to FTC data request, 1956.

only if Pfizer were to exercise its option to take a license under any Bristol patents relating to the subject matter described in (*a*), (*b*), (*c*), and (*d*) above. It was agreed that purchasers of tetracycline in bulk from Bristol could either pay royalty directly to Pfizer or that such royalty could be paid by Bristol for its bulk customers (Olin Mathieson and Upjohn). In the latter situation, royalty payable by Bristol would be computed on the basis of tetracycline's "presumed sales value" by the bulk customers.

On the date of the execution of this agreement, Bristol paid to Pfizer a liquidated sum "representing the minimum estimated royalties due to Pfizer hereunder on the operations of Bristol, its subsidiaries, affiliates, and bulk customers, during the period from January 11, 1955, through December 31, 1955," and it was agreed that, on or before April 30, 1956, Bristol should pay to Pfizer any excess of the calculated royalties on such operations over such estimated sum.

A noncontestability clause was included in the settlement:

> Neither party shall contest the validity of any claim * * * included in licensed patents nor voluntarily assist others in any infringement thereof or in the defense of any suit brought for such infrigement. Such obligations shall not take effect with respect to any patent claim until it is included within the licensed patents and shall remain in effect until termination or cancellation of the license thereunder * * *."

The agreement also contained an arbitration clause for the settlement of disputes.

The Pfizer-Olin Mathieson agreement; The Pfizer-Upjohn agreement: These two licensing agreements are essentially identical. In each of them, Pfizer as "licensor hereby grants to the licensee its subsidiaries and affiliates, a nonexclusive right and license under the licensed patent rights, to purchase, compound, and use licensed products and to sell the same in the form of therapeutic tetracycline to the drug trade." [97] Provisions for payment of royalty by each licensee are detailed. Basically, Pfizer is to be paid a specified percentage of either the "net sales price" or the "presumed sales value" of tetracycline sold by each licensee. Under each licensing agreement—

> It is understood that no royalties need be paid by licensee, its subsidiaries or affiliates, on their sales or use of licensed products to the extent that such royalties are paid by Bristol Laboratories, Inc., a New York corporation having an office at 630 Fifth Avenue, New York, N. Y. * * *.

There are other provisions in the agreements binding the licensees never to contest any claim included in the licensed patent rights and

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[97] Agreement dated March 28, 1956, between Chas. Pfizer & Co., Inc., and The Upjohn Company. Agreement dated March 28, 1956, between Chas. Pfizer & Co., Inc., and Olin Mathieson Corp. Both agreements were submitted to the Federal Trade Commission in response to FTC data request, 1956.

binding the parties to settle by arbitration any disputes arising out of the agreements.

The Pfizer-Olin Mathieson and Pfizer-Upjohn agreements are limited to licensing of the tetracycline product claims of U. S. Patent 2,699,054 owned by Pfizer. There were no cross-licensing provisions, and neither of the two licensees was empowered to grant any sublicenses in the United States or abroad.

CHAPTER IX

Trademarks and Fair Trade in the Antibiotics Industry

Trademarks and Trade Names

A trademark is defined in the Federal Trademark Act of 1946 (the Lanham Act) as—

> * * * any word, name, symbol, or device or any combination thereof adopted and used by a manufacturer or merchant to identify his goods and distinguish them from those manufactured or sold by others.[1]

Trade names are defined in the Lanham Act to include—

> * * * individual names and surnames, firm names and trade names used by manufacturers, industrialists, merchants, agriculturists, and others to identify their businesses, vocations, or occupations; the names or titles lawfully adopted and used by persons, firms, associations, corporations, companies, unions, and any manufacturing, industrial, commercial, agricultural, or other organizations engaged in trade or commerce and capable of suing and being sued in a court of law.[2]

Examples of trademarks which will be encountered in this chapter are such coined words as Ilotycin, the trademark used by Eli Lilly & Co. to designate products containing erythromycin, and Chloromycetin, the trademark used by Parke, Davis & Co. to designate products containing chloramphenicol. Examples of trade names used in the antibiotics industry are UPJOHN, ABBOTT, and BRISTOL, representing the Upjohn Co., Abbott Laboratories, and Bristol Laboratories, Inc.

The primary function of a trademark or trade name is to identify a product or to identify the source or origin of that product. It is this identification function which has molded the law of trademarks.[3] However, to the extent that manufacturers succeed, through advertising and promotion of their trademarked or branded products, in differentiating their products in the minds of consumers from other like or similar products manufactured by competitors, a degree of power in controlling sales of those products in the market is achieved.

[1] 15 U. S. C. A. § 1127.
[2] 15 U. S. C. A. § 1127.
[3] Rudolph Callmann, "Trademark Infringement and Unfair Competition," Law and Contemporary Problems, vol. 14, No. 2, spring 1949, p. 185.

The hope or expectation of creating such a preference for his product is the basis for a manufacturer's willingness to spend large sums of money advertising his goods. In effect, the advertiser is striving to create a symbol which purchasers will recognize and to which they will react. In the words of Mr. Justice Frankfurter:[4]

> If it is true that we live by symbols, it is no less true that we purchase goods by them. A trademark is a merchandising shortcut which induces a purchaser to select what he wants, or what he has been led to believe he wants. The owner of a mark exploits this human propensity by making every effort to impregnate the atmosphere of the market with the drawing power of a congenial symbol. Whatever the means employed, the aim is the same—to convey through the mark in the minds of potential customers the desirability of the commodity upon which it appears. Once this is attained, the trademark owner has something of value. If another poaches upon the commercial magnetism of the symbol he has created, the owner can obtain legal redress.

In 1943 there were no trademarks to indicate manufacturers of antibiotic products; there were only 2 or 3 known antibiotics, of which penicillin was the most important. At that time very little penicillin was being produced, and little or none was available for civilian use, all supplies going to the Armed Forces.

By 1954 over 100 different antibiotic preparations were marketed under at least 550 different trademarks and trade names.[5] No supplemental listing of antibiotic trademarks and trade names has been compiled since that date, but undoubtedly there has been a numerical increase in antibiotic preparations, and in the trademarks and trade names under which they are sold.

All clinically useful antibiotics have generic names. When sold commercially they are normally sold under registered trademarks, although some companies have marketed certain antibiotics, penicillin products for instance, under their generic names accompanied by the trade names of the marketing companies. The leading manufacturers of antibiotics have trade names, which are registered in the Patent Office in the same manner as trademarks used on specific products.

Vice President W. G. Malcolm, of American Cyanamid Co., stated on October 4, 1955, that over $20 million had been spent by his company as of that date in advertising Aureomycin.[6] Vice President Thomas J. Winn, of Chas. Pfizer and Co., stated on August 5, 1952, that between January 27, 1950, and August 1952, Pfizer spent $7½ million in the advertising and promotion of Terramycin.[7]

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[4] *Mishawaka Rubber and Woolen Mfg. Co.* v. *S. S. Kresge Co.*, 316 U. S. 203, 205, 62 S. Ct. 1022 (1942).

[5] Henry Welch, "The Manual of Antibiotics, 1954–55," Medical Encyclopedia, Inc., New York: 1954, pp. 77–82 and 83–84.

[6] Trademark Registration File No. 639,933, affidavit of W. C. Malcolm, dated October 4, 1955.

[7] Trademark Registration File No. 577,504, affidavit by Thomas J. Winn, dated August 5, 1952.

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These amounts spent on advertising by Pfizer and Cyanamid, in their efforts to create goodwill for their respective products, indicate the value which trademarks may represent.

Because the physician rather than his patient selects the antibiotic that will be used, advertising of antibiotics is directed to physicians and the retail sellers, the pharmacists. In selling their products, antibiotics manufacturers direct particular attention to insuring that their trademarks and trade names are known to physicians and pharmacists.

The American Medical Association expressed concern during the late 1940's because of the great number of penicillin trademarks in use. In a 1946 editorial entitled "Silly Names for Penicillin Products," the association's Journal complained in the following terms:[8]

> Instead of selling penicillin under its simple and well-known name, they have become downright silly and offer penicillin under so many names that only a professional solver of crossword puzzles could guess the nature of the products that these names conceal.
>
> The promulgators of these products and their sale are interested in helping their own pocketbook by trying to make certain that the prescribing physician will limit himself to their products. One manufacturer naively combines his firm name with "cillin." There are more than 20 manufacturers. Carried to a logical conclusion that would give us not only "Ledercillin" but also "Squibbcillin," "Abbottcillin," "Schenleycillin," "Commercial Solventscillin," plus some others.

The increasing number of trademarks and trade names used to designate antibiotic products led to publication in 1954 of The Manual of Antibiotics, an 87-page book, devoted exclusively to listing the trademarks and trade names under which preparations of the various antibiotics are sold. In the preface it is stated:

> Over the past few years the number of trade names used for antibiotic preparations has increased tremendously. * * * Because of this multiplicity of trade names it has become practically impossible for the physician, pharmacist, and others engaged in the use of these drugs to remember just what the composition of the product is from the trade names.[9]

The Manual of Antibiotics is at present in process of revision to include the many new antibiotic preparations which have reached the market since its original publication. In the area of combinations of antibiotics alone, more than 60 new preparations have been made available since 1954.[10]

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[8] Journal of the American Medical Association, editorial, February 2, 1946, No. 130, p. 279. Two years later, in July 1948, the Journal reiterated its objection to the penicillin trademark situation with the publication of an editorial announcing the existence of "More Silly Names for Penicillin Products," listing 17 samples of recently marketed penicillin products bearing trademarks. (The Journal of the American Medical Association, editorial, July 17, 1948, vol. 137, p. 1043.)

[9] Henry Welch, The Manual of Antibiotics, 1954–55, Medical Encyclopedia, Inc., New York, 1954, Preface.

[10] Henry Welch, "Further Comments on Combined Therapy," Antibiotic Medicine & Clinical Therapy, January 1957, p. 21, footnote.

Penicillin

Table 66, below, lists certain trademarks under which procaine penicillin was sold in 1956. For purposes of preparation of this table, the 300,000-unit dosage form of procaine penicillin in aqueous suspension was selected. This particular dosage form of procaine penicillin is marketed by at least 23 different companies. Ten of these companies have individual trademarks for this product; the remainder of the companies market the product under its generic name and their respective trade names.

Of the 10 companies marketing procaine penicillin under trademarks in 1956, 5 were original manufacturers of this product. These companies were Squibb Division of Olin Mathieson Chemical Corp., Eli Lilly & Co., Bristol Laboratories, Inc., Sharp & Dohme Division of Merck & Co., and Wyeth Laboratories. The remaining five companies purchased procaine penicillin in bulk, packaged it into dosage forms, and resold it under their own trademarks.

TABLE 66.—*Procaine penicillin in aqueous suspension*

Trademark	*Company*
Crysticillin, 300 A. S	E. R. Squibb & Sons, Inc. (division of Olin Mathieson Chemical Corp.).
Crysticillin unimatic, 300 A. S. (disposable unit).	Do.
Diurnal, penicillin readimixed, 300 M	The Upjohn Co.
Dorsallin, A. R	Smith-Dorsey Co.
Duracillin, A. S	Eli Lilly & Co.
Flo-Cillin, aqueous	Bristol Laboratories, Inc. (subsidiary of Bristol-Myers Co.).
Hydracillin	Premo Pharmaceutical Laboratories, Inc.
Ledercillin suspension	Lederle Laboratories (division of American Cyanamid Co.).
Parencillin in aqueous suspension	Wm. S. Merrell Co.
Sharcillin aqueous	Sharp & Dohme, Inc. (division of Merck & Co., Inc.).
Wycillin suspension	Wyeth Laboratories, Inc. (division of American Home Products Corp.)

Source: Henry Welch, The Manual of Antibiotics, 1954–55, Medical Encyclopedia, Inc., New York, 1954, p. 33, and The American Druggist Blue Book, 1956–57. The original source listing trademarks for this product was The Manual of Antibiotics, 1954–55. The American Druggist Blue Book, 1956–57, was checked in order to make sure that these products were still being marketed in 1956.

Thirteen companies marketed this dosage form of procaine penicillin under its generic name and their respective trade names in 1956.[11] Only two of the companies selling under their trade names were original manufacturers of procaine penicillin: Abbott Laboratories and Chas. Pfizer & Co., Inc.

[11] These companies were Abbott Laboratories, Bio-Ramo Drug Co., George A. Breon & Co., Chase Chemical Co., Lannett Co., Martin Drug Co., The S. E. Massengill Co., Parke, Davis & Co., Chas. Pfizer & Co., Inc., Siler Medical Corp., Veltex Chemical Co., Vitamix Corp., and Winthrop Chemical Co.

The trademarks presented in table 66 all represent the same basic procaine penicillin preparation. There are at least 10 additional preparations containing 1 of the 3 common salts of penicillin (procaine, sodium, or potassium), and most of these preparations are sold under a number of different trademarks.

The prices of various companies for 3 penicillin dosage forms are set out in tables 43, 44, and 45. These tables do not present any consistent pattern of differences between the prices of the larger manufacturers which might be expected to have been most successful in promoting their trade names or trademarks and the packagers. The published prices of the manufacturers for buffered potassium penicillin tablets (table 45) were identical but in all instances appreciably higher than those of the packagers. The same situation does not obtain as to the procaine penicillin dosage forms compared in table 44 (aqueous suspension) and table 44 (tablet form).

The prices of 9 sellers including 3 manufacturers and 6 packagers of 3 million units in aqueous suspension (10 units) for 1956 are listed on page 172. The prices of 3 of the manufacturers for this form were identical at $0.19, which is 4 cents more than the lowest price quoted by any packager but 26 cents lower than the highest price of any packager. The price of Lederle, as indicated on page 172, was 31 cents.

Likewise, the 1956 published prices of 1 manufacturer and 5 packagers for procaine penicillin in tablet form do not show the prices of the former as higher than all of those of the latter.

Although 3 of the packagers quoted prices considerably less than those of the manufacturer, the prices of the fourth packager, Vitamix, approximated those of Lilly, an original manufacturer, and Lederle, which, although an original manufacturer of some antibiotics, is a packager and compounder of procaine penicillin.

Several penicillin types are marketed by only a few companies. Among these are benzathine penicillin, phenoxymethyl penicillin, and hydrabamine penicillin. All of these products are distributed under the trademarks of their respective manufacturers. Table 67 lists the generic names, manufacturers, and trademarks for these penicillins.

TABLE 67.—*Generic names, manufacturers and trademarks of certain penicillin types*

Generic name	Manufacturer	Trademark
Benzathine pencillin	Eli Lilly & Co	Neolin.[1]
	Chas. Pfizer & Co., Inc	Permapen.
	Bristol Laboratories	Penbiotic.[1]
	Wyeth Laboratories	Bicillin.
Phenoxymethyl penicillin	Eli Lilly & Co	V-Cillin.
	Wyeth Laboratories	Pen-Vee.
Hydrabamine penicillin	Abbott Laboratories	Compocillin V.

[1] Combinations of benzathine pencillin with other substances.

Penicillin products are characterized by a variety of trade names and trademarks to a much greater extent than any of the other antibiotics in general use. There are comparatively few trademarks for streptomycin and dihydrostreptomycin. The sulfates of streptomycin and dihydrostreptomycin are sold under their generic names, in connection with the trade name of the seller.

Erythromycin

Erythromycin is sold by only three companies, and one of these, The Upjohn Co., distributes the more important dosage forms under the generic name erythromycin. Eli Lilly & Co.'s trademark for erythromycin is Ilotycin, and the trademark of Abbott Laboratories is Erythrocin.

Broad spectrum antibiotics

Three of the broad spectrum antibiotics are sold by only one manufacturer and under one trademark only. A fourth, tetracycline, is distributed by 5 companies, of which 3 are original manufacturers. All five distributors sell the product under their respective trademarks. The generic names of the broad spectrum antibiotics, and the trademarks under which they are sold, are presented in table 68.

Novobiocin

Novobiocin, which in 1956 ranked along with erythromycin and some of the broad spectrum antibiotics in total dollar sales, is sold by The Upjohn Co. as Albamycin, and by Merck & Co., Inc., under the trademark Cathomycin.

TABLE 68.—*Generic names and trademarks of the broad spectrum antibiotics*

Generic name	Company	Trademark
Chlortetracycline	American Cyanamid Co	Aureomycin.
Chloramphenicol	Parke, Davis & Co	Chloromycetin.
Oxytetracycline	Chas. Pfizer & Co., Inc	Terramycin.
Tetracycline	Original manufacturers:	
	American Cyanamid Co	Achromycin.
	Chas. Pfizer & Co., Inc	Tetracyn.
	Bristol Laboratories, Inc	Polycycline.[1]
	Manufacturing distributors:	
	E. R. Squibb & Sons (division of Olin Mathieson Chemical Corp.).	Steclin.
	The Upjohn Co	Panmycin.

[1] Bristol Laboratories trademark for tetracycline phosphate is Tetrex.

Combinations

All of the antibiotics discussed in the foregoing pages are packaged into dosage forms and sold as individual products. In addition, most of these antibiotics are marketed in prepared dosage forms either in combination with other antibiotics or in combination with various

other drug products. Combination products of this sort are marketed under trademarks in the same manner as are the particular antibiotics when packaged alone.

Table 69, below, lists nine trademarks used to designate and advertise one particular dosage form containing penicillin and dihydrostreptomycin in combination.

TABLE 69.—*Penicillin and dihydrostreptomycin*

[Active ingredients: 300,000 units/dose procaine penicillin G; 100,000 units/dose sodium or potassium penicillin G; 0.5 gram dose dihydrostreptomycin base]

Trademark or trade name	Company
Cillimycin 0.5	Wyeth Laboratories, Inc.
Combiotic P-S 0.5 GM Formula	Chas. Pfizer & Co., Inc.
Dicrysticin	E. R. Squibb & Sons, Inc.
Dihydrocillin, Fortified, 1/2	The Upjohn Co.
Fortimycin, H. S	Premo Pharmaceutical Laboratories, Inc.
Pen-Aqua	Bristol Laboratories, Inc.
Penimycin	Liberty Vitamin Co.
Penstrip "4 :1/2"	Sharp & Dohme, division of Merck Company, Inc.
Synergistin	Consolidated Midland Corp.

Source: Henry Welch, The Manual of Antibiotics, 1954–55, Medical Encyclopedia, Inc., New York, 1954, p. 33, and the American Druggist Blue Book, 1956–57. The original source listing trademarks for this product was The Manual of Antibiotics, 1954–55. According to the American Druggist Blue Book, 1956–57, these products were still being marketed in 1956.

In 1954 there were 15 or more different combinations of antibiotics, each of which was marketed under one or more trademarks. Most of these combinations of products containing antibiotics other than penicillin, streptomycin, or dihydrostreptomycin consisted of ointment or lozenge preparations comprising two or more relatively minor antibiotics, as, for example, bacitracin, neomycin, polymyxin, and tyrothricin.[12]

As previously noted, since 1954 at least 60 new combinations containing one or more antibiotics have appeared on the market. Examples of trademarks used to designate these combinations are Sigmamycin (tetracycline and oleandomycin), Mysteclin (tetracycline and nystatin), and Cathocillin (novobiocin and penicillin). There seems to be a trend toward the marketing of dosage forms containing fixed combinations of antibiotics intended for systemic use.

Trademarks or trade names may serve a useful function as easily pronounced short names for frequently complex combination products. The Rhodes Pharmacal Co., Inc., for example, markets a tyrothricin ointment under the name Predicaine, containing tyrothricin (0.5 mg., 1 gm.), benzocaine (5.0 percent), p-chlor-m-xylenol (1.0 percent), and methylbenzathonium chloride (0.6 percent). Tetrazets, the trademark of Sharp & Dohme Division of Merck & Co., is the only name under which troches containing bacitracin (50 units/troche),

[12] For a listing of antibiotic combinations marketed in 1954, see Henry Welch, The Manual of Antibiotics, 1954–55, Medical Encyclopedia, Inc., New York, 1954.

neomycin sulfate (5 mg.), tyrothricin (1 mg.), and benzocaine (5 mg.) are marketed.

Many more examples of the utility of trade names as short names for complex preparations containing several drugs in combination could be cited.

The Commission's antibiotics study has been confined to production and sales in the United States. It should be pointed out here, however, that trademarks and trade names may be even more important in sales abroad. This is because in certain foreign countries it is impossible to obtain patent protection on medicinal products, and in such cases trademarks and trade names may be of great significance in obtaining and holding a market.

Fair Trade in the Antibiotics Industry

Prior to passage of the Miller-Tydings Act in 1937, it was a violation of the Federal antitrust laws for manufacturers whose products are sold in interstate commerce to enter into agreements fixing minimum resale prices. "Vertical" price-fixing arrangements [13] of this nature were held to be in violation of the Sherman Antitrust Act by the United States Supreme Court in 1911 in the case of *Dr. Miles Medical Co.* v. *John D. Park & Sons Co.*[14] The court pointed out that "vertical" arrangements between a manufacturer and retail sellers of his goods could eliminate competition as effectively as "horizontal" agreements among the retailers themselves.[15]

During the depression years many State legislatures enacted "fair trade" laws permitting "vertical" price fixing on intrastate sales of trademarked or branded goods.[16]

In 1937 the United States Congress amended the Sherman Act by passing the Miller-Tydings Act which exempts the following from the Federal antitrust laws:

> Contracts or agreements prescribing minimum prices for the resale of a commodity which bears, or the label or container of which bears, the trademark, brand, or name of the producer or distributor of such commodity and which is in free and open competition with commodities of the same general class pro-

[13] In Ewald T. Grether, Price Control Under Fair Trade Legislation, Oxford University Press, New York, 1939, p. 4, "Vertical" price control is defined as "a price constraint between sellers on different levels, as for instance between manufacturers and wholesalers, manufacturers and retailers, or wholesalers and retailers. The most pronounced form of vertical price control has long been known as 'resale price maintenance.' Horizontal price control is defined as a constraint between sellers on a given level. For instance, when retailers in a local market employ measures of price regulation by agreement among themselves, this activity would be classified as 'horizontal'; if manufacturers put the device into effect for the retailers the procedure would be classified as 'vertical.' "

[14] 220 U. S. 373 (1911).

[15] *Dr. Miles Medical Co.* v *John D. Park*, 220 U. S. 373, 408 (1911).

[16] In the Federal Trade Commission's Report on Resale Price Maintenance, 1945, pp. 4–10, the economic factors leading to passage of the State resale price maintenance statutes are discussed at length.

duced or distributed by others, when contracts or agreements of that description are lawful [in the State of resale].[17]

After this statute had been held not to control distributors who had not signed contracts directly with the manufacturer, Congress in 1952 passed the McGuire Act. The McGuire Act, which amends the Federal Trade Commission Act, is in many respects similar to the Miller-Tydings Act, but is broader in scope.

The McGuire Act legalizes contracts prescribing both minimum and stipulated prices, whereas the Miller-Tydings Act provided only for minimum prices. Moreover, the McGuire Act provides for nonsigner clauses making it lawful to compel, by an action under State fair trade laws, noncontracting as well as contracting parties to abide by fair trade prices established in the State.

The constitutionality of the McGuire Act has never been squarely tested in the United States Supreme Court, although certiorari was denied in one case. (*Schwegmann Bros. Giant Supermarket* v. *Eli Lilly & Co.*, 346 U. S. 856, 74 S. Ct. 71 (1953).) However, the highest courts in 14 States have held that their fair trade acts, insofar as they applied to non-signers, are unconstitutional. In four more States there are lower court decisions to the same effect, making a total of 18 States in which the nonsigner aspect has been declared unconstitutional. Since 3 States and the District of Columbia have no fair trade laws, and in 9 more States the laws have not been tested by the courts, these figures become even more significant. Moreover, courts in four States have declared their fair trade acts in general unconstitutional. The primary reason given by most State supreme courts for holding the fair trade laws, as applied to nonsigners, unconstitutional was that they violated the due process clause of the State constitution.

Many of the large manufacturers of antibiotics have established minimum resale prices at either the wholesale or the retail level, or both, for many of their antibiotic products. Some samples of the use of fair trade in the antibiotics industry are noted as to certain products:

Chloromycetin

This product is manufactured exclusively by Parke, Davis & Co. The 1956–57 edition of Antibiotics Annual reports that "Chloramphenicol (Chloromycetin) at present is the drug of choice the world over for typhoid fever."[18]

Fair trade prices established by Parke, Davis & Co. for this product are listed in table 70, which follows.

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[17] 15 U. S. C. sec. 1.

[18] Sam S. Woolington, Sidney S. Adler, and Albert G. Bower, "Five Years Experience With Chloramphenicol," Antibiotics Annual, 1956–57, edited by Henry Welch and Felix Marti-Ibanez, Medical Encyclopedia, Inc., New York, 1957, p. 371.

TABLE 70.—*Chloromycetin published fair-trade prices: 1956–57*

Type of preparation	Retail fair-trade minimum	Wholesale price to retailer	Percentage markup on cost
Capsules:			
50-milligram:			
Bottle of 25	$2.87	$1.91	50.26
Bottle of 100	10.71	7.14	50.00
100-milligram:			
Bottle of 25	5.42	3.61	50.14
Bottle of 100	20.65	13.77	49.96
Cream, 1 percent, 1-ounce tube capacity	1.66	1.11	49.55
Intramuscular, 1 centimeter steri-viol., each	3.60	2.40	50.00
Kapseals, 250-milligram:			
Bottle of 16	7.65	5.10	50.00
Bottle of 100	45.91	30.60	50.03
Opthalmic, 25-milligram vial w/dropper, each	1.21	.81	49.38
Otic, 15 cubic centimeter vial w/dropper, each	2.02	1.35	49.63
Palmitate, suspension oral 60 cubic centimeter bottle, each	3.82	2.55	49.80

Source: American Druggist Blue Book, 1956–1957, American Druggist, New York, 1956, p. 152.

Aureomycin

Aureomycin (Chlortetracycline) is manufactured and sold exclusively by Lederle Laboratories Division of American Cyanamid Co.,[19] owner of a patent on this product.

Table 71 presents the fair trade minimum price published for Aureomycin, specifies the wholesaler's price to the retailer, and shows the percentage markup.[20]

TABLE 71.—*Aureomycin published fair-trade prices: 1956–57*

Type of preparation	Retail fair-trade minimum	Wholesale price to retailer	Percentage markup on cost
Capsules:			
50-milligram:			
Package of 25	$2.86	$1.91	49.74
Package of 100	10.71	7.14	50.00
100-milligram:			
Package of 25	5.42	3.61	50.14
Package of 100	20.65	13.77	49.96
250-milligram:			
Package of 16	7.65	5.10	50.00
Package of 100	45.90	30.60	50.00
Intravenous vial:			
100-milligram, each	1.16	.77	50.65
250-milligram, each	2.43	1.62	50.00
500-milligram, each	4.36	2.91	49.83
Ophthalmic ointment 1 percent, 6 tubes ⅛ ounce each	1.83	1.22	50.00
Otic, package, each	1.83	1.22	50.00
Nasal, 10-milligram vial w/dropper	1.12	.75	49.33
Rectal suppositories, 50-milligram jar of 8 each	2.52	1.68	50.00

The percentage markup on cost necessary to comply with the fair trade prices ranges from 49⅓ percent (Aureomycin for nasal application) to 50⅔ percent (Aureomycin for intravenous injection).

[19] As previously mentioned, Bristol Laboratories, Inc., has the right to manufacture and sell a tetracycline product containing up to 6 percent chlortetracycline.

[20] Source: American Druggist Blue Book, 1956–57, published by American Druggist, New York, 1956, pp. 99–100.

Erythromycin

Three companies manufacture and sell this antibiotic: the patent owner, Eli Lilly & Co., and two licensees, Abbott Laboratories and the Upjohn Co. Table 72 specifies the minimum resale prices which have been published for Erythromycin Lactobionate, an erythromycin preparation sold by Abbott Laboratories only.[21]

TABLE 72.—*Erythrocin lactobionate published fair trade prices: 1956–57*

Type of preparation	Retail fair-trade minimum	Wholesale price to retailer	Percentage markup on cost
Vials, sterile:			
300-milligram, each	$2.85	$1.90	50.00
1 gram, each	7.51	5.00	50.20

This table shows that the retail druggist pays $1.90 for a 300-milligram vial of Erythrocin Lactobinate; the fair trade selling price is $2.85, a 50-percent markup on cost. For the 1-gram sterile vial, the pharmacist or druggist pays $5; the consumer price is $7.51, a 50.2-percent markup on cost.

[21] Source: American Druggist Blue Book, 1956–57, The American Druggist, New York, 1956, p. 228.

CHAPTER X

Antibiotics and the Public

During 1943–1945, the very limited allocations of penicillin which could be made for civilian use were made by the Government. On March 15, 1945, distribution to civilians through normal channels began.

What the public has spent for penicillin and other antibiotics during the succeeding years, and what it has obtained in longer life and better health, are matters for conjecture. While national studies of medical costs have been made, and a number of samplings of expenditures for drugs and medicines have been conducted, spending for antibiotics or for antibiotics prescriptions has not been surveyed on a national basis.

Consumer Purchases of Antibiotics

In terms of production less exports, about 645 metric tons of antibiotics were used in the United States in 1956, at a rate of nearly 4 grams for each person in the entire population. In 1950, purchases were at the rate of less than 1 gram per person. Table 73 shows estimated United States consumption of antibiotics (quantity of manufacturers' sales minus exports) for the years 1950 through 1956, and the annual percentage increase in consumption.

TABLE 73.—*Estimated United States consumption of antibiotics: 1950 to 1956*

[In metric tons]

Year	Manufacturers'—		United States consumption [1]	Percent increase in consumption over previous year
	Sales	Exports		
1950	326.2	186.4	139.8	------
1951	568.4	275.2	293.2	109.7
1952	663.3	243.8	419.5	43.1
1953	800.2	276.4	523.8	24.9
1954	919.1	380.2	538.9	2.9
1955	998.6	371.7	626.9	16.3
1956	1,051.1	405.9	645.2	2.9

[1] There is an indeterminate amount of spoilage affecting these totals, for which no adjustment has been made.

Source: FTC data requests, 1956 and 1957; U. S. Department of Commerce, United States Exports of Domestic and Foreign Merchandise, Report No. FT 410, pt. II, for years 1950–56, Washington, D. C.

The manufacturers' sales for United States consumption shown above include both antibiotics of medicinal grade and antibiotics of animal feed grade. Nearly all of the medicinal grades sold by prescription, or administered by the medical profession. The exceptions are certain ointments and lozenges that contain only small quantities of antibiotics and are not significant in the total picture.

Medicinal grade antibiotics accounted for all sales until 1950. In that year, for the first time, small amounts of antibiotics were sold for use in animal feed supplements, and other sales for minor uses have been made since that time.[1]

The cost to the public of these purchases of antibiotics has been estimated but precise data are not available. It is known that prescription forms account for the largest portion of total spending. This can be determined from manufacturers' dollar sales, about 90 percent of which represented medicinal grade antibiotics (which, as stated above, normally require prescriptions) in both 1955 and 1956. (See chart 6B, p. 81.)

Estimates of consumer spending on all grades of antibiotics in 1953 have been placed at $575 million by the Manufacturing Chemists' Association.[2] An estimate of the spending on antibiotics for human therapy alone, for the year 1957, was placed at $750 million.[3]

Antibiotic prescriptions

Since antibiotics first became available for civilian use in 1945, they have grown steadily in importance as prescription items, with most of their growth occurring since 1948. According to information from trade sources it appears that, in 1948, antibiotic prescriptions accounted for only 1.5 percent of the total number written; in 1952, 13.7 percent; in 1954, 17.2 percent; and in 1955, they accounted for 12.7 percent of the total number written.[4]

In 1955, $1,258 million is reported to have been spent by the Nation on prescriptions.[5] Of the 577 million prescriptions written in that year,[5a] antibiotics were reported to have been called for in 73 million, or 12.7 percent of the total number written.[6] The total number of

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[1] Table 7, p. 68, lists the kinds and quantities of antibiotics sold as animal feed supplements in 1956. Chart 3, p. 71, shows the comparisons between output of different grades through the span of years from 1948 to 1956.

[2] The Chemicals Industry Facts Book, Manufacturing Chemists' Association, Washington, 1955, p. 40.

[3] Statement made at the Pasteur Fermentation Centennial in New York, 1957, entitled "What's Ahead in Fermentation," Chemical & Engineering News, vol. 35, No. 48, Dec. 2, 1957, p. 47.

[4] Modern Medicine Topics, vol. 17, No. 5, May 1956; and Journal of the American Pharmaceutical Association, vol. 18, No. 5, May 1957, p. 262; The Chain Store Age, December 1956; Pharmaceutical Review.

[5] Drug Topics, vol. 100, No. 16, New York, August 6, 1956, p. 18.

[5a] Journal of the American Pharmaceutical Association, vol. 18, No. 5, May 1957, p. 262.

[6] "Antibiotics: Have we entered a third era?" The Chain Store Age, Dec. 1956, Pharmaceutical Review.

prescriptions increased to 585,920,000 in 1956 and 641,330,000 in 1957[7] but the number calling for antibiotics has not been reported by trade sources.

The average price of all prescriptions has been variously estimated, but, again, no national data are available upon which to base an estimate of the average cost of an antibiotic prescription.

A prescription survey made in 1954–55 placed average prices of all prescriptions at $2.36 and the median price at $1.41.[8] Another survey in 1954 revealed an average prescription price of $2.27.[9] The average prescription price in 1956 has been reported as $2.49, and in 1957 had increased to $2.64.[10]

Antibiotics used in medical therapy, when prescribed for oral administration are purchased from the druggist upon presentation of a doctor's prescription. Antibiotics may also be given by injection in the doctor's office or in the hospital. When an injection is given, the physician charges a fee for professional services which includes his charge for the antibiotic.

During 1956, the single medicinal antibiotic produced and sold in the largest volume was procaine penicillin. This substance is usually administered by injection, and the most common single vial provides 300,000 units of procaine penicillin per injection dose of 1 cubic centimeter. The published retail prices for procain penicillin in vials containing 10 injections of 300,000 units each range from 94 cents to $1.73.

A great variety of antibiotics, especially the newer ones, are suitable for oral dosage. These are prescribed by the doctor in varying amounts and purchased by the patient at the drugstore. The prescription may call for several days' supply or longer, depending on the condition or purpose for which prescribed. Therefore, the price of the prescription may vary according to the doctor's prescribed course of medication, and in some cases according to the particular antibiotic prescribed.

Table 74 lists some of the more widely published prescription items and shows the published retail price. The price for each capsule or tablet, usually 250 milligrams of the particular item, is shown in a third column. The price per tablet or price per capsule does not indicate a dosage price, for the doctor may signify that more than one capsule or tablet should be taken at a time. Neither does this third column indicate a price for a course of treatment because the number of capsules per dose, the number of doses, and the days of

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[7] Drug Trade News, vol. 33, No. 5, March 10, 1958, p. 16.

[8] National Prescription Survey, 1954–55, Brooklyn College of Pharmacy, New York, pp. 6 and 7.

[9] The Lilly Digest, 23d annual edition, 1954, Eli Lilly & Co., Indianapolis, Ind., p. 26.

[10] Drug Trade News, vol. 33, No. 5, March 10, 1958, p. 16.

treatment will depend on the duration and severity of the condition for which prescribed.

TABLE 74.—*Published prices of certain antibiotics prescription (oral) forms: 1956*

Prescription	Published retail price	Price per capsule or tablet
Tetracycline:		
"Tetracyn" capsules, 250-milligram, 16's	$8.50	$0.53.
"Achromycin" capsules, 250-milligram, 16's	$7.65 to $8.50	$0.48 to $0.53.
"Polycycline" capsules, 250-milligram, 16's	$8.50	$0.53.
"Steclin" capsules, 250-milligram, 16's	$7.65 to $8.50	$0.48 to $0.53.
"Panmycin" capsules, 250-milligram, 16's	$7.56	$0.47.
Oxytetracycline: "Terramycin" capsules, 250-milligram, 16's.	$8.50	$0.53.
Chlortetracycline: "Aureomycin" capsules, 250-milligram, 16's.	$7.65 to $8.50	$0.48 to $0.53.
Erythromycin:		
"Ilotycin" tablets, 100-milligram, 36's	$7.78 to $8.64	$0.22 to $0.24.
"Erythromycin" tablets, 200-milligram, 25's	$11.25	$0.45.
Chloramphenicol: "Chloromycetin" capsules, 250-milligram, 16's.	$7.65 to $8.50	$0.48 to $0.53.
Penicillin V:		
"Pen Vee" tablets, 300-milligram, 12's	$4.32 [1]	
"V-cillin" capsules, 250-milligram, 24's	$10.80 to $12.00	$0.45 to $0.50.
Penicillin G, potassium buffered: 250,000 units, 12 tablets (Abbott).	$2.25	$0.19.
Penicillin G, procaine buffered: 250,000 units, 12 tablets (Lederle).	$2.65	$0.22.

[1] Wholesale price; retail price not published.

Source: Drug Topics Red Book, Topics Publishing Co., Inc., New York, 1956 and 1957.

Antibiotic prescription forms are increasingly being prepared as mixtures of one or more antibiotics, or as mixtures of antibiotics with sulfa or other drugs. Sometimes the antibiotic substance is only a minor ingredient in the prescription. The many combinations in which antibiotics are prepared by manufacturers are not shown in table 74, which lists only a few of the one-substance forms of prescriptions. Because of the varieties and combinations of antibiotics prepared in prescription forms, it is impossible to determine, in many cases, the principal cost element in the prescription. A comparison between the cost of different antibiotic prescriptions is further complicated, as already indicated, by variations in dosages and in the ways in which antibiotics are used by the medical profession.

Antibiotics have ranked as the leading ingredient of prescriptions in virtually every fortnightly survey made by the American Druggist magazine since 1952. In the few instances when antibiotics have dropped to second place among the eight categories of drugs prescribed, they have been outranked only briefly by barbiturates.

Antibiotics have also led other prescription ingredients in numbers of new specialties introduced annually. Table 75, taken from Chain Store Age, shows trends since 1953 in numbers of new prescription specialties offered. The year 1956, not shown on the table, marked the introduction of an unusually large number of new specialities.

TABLE 75.—*Number of new prescription specialties introduced: 1953, 1954, and first 6 months of 1955*

Product classification	1953	1954	1955, 1st 6 months
Antibiotics—sulfas and combinations	51	79	34
Vitamins, minerals, hemantics, lititropics, etc	50	67	36
Sedatives, hypnotics, analgesics, etc	43	52	48
Hormones	42	38	33
Gastrointestinals	27	26	11
Cardiovasculars	22	59	13
Autonomics	15	9	----
Antihistaminics	10	29	6
Gynecologicals	9	----	8
Cough and cold	6	16	7
Central nervous system stimulants	4	----	5
Biologicals	----	10	9
All other	57	35	18

Source: 1956 Modern Medical Market Guide, Modern Medicine Publications, Inc., Minneapolis, Minn., 1956, p. 38, from Drug Executives Edition, Chain Store Age.

Public Health

Many factors affect public health data on death rates and incidence of diseases. Although a direct connection between these data and the advent of antibiotics cannot be shown, comparisons in death and disease rates for the period before antibiotics and the period after the use of antibiotics are believed to be significant.

The area where antibiotics have made the most important contribution to public health is unquestionably in the treatment of infections and contagious diseases. Many diseases of this kind are caused by bacteria which succumb to the action of antibiotics. In this field, antibiotics have been called "catastrophic" medicines because of their dramatic effectiveness in many serious infections on battlefields, in surgery, and in accidents. They have also proven effective in preventing complications that often follow severe illnesses even when the original illness was not responsive to antibiotics therapy. The "complication," which formerly might have caused the patient's death because of its cumulative effect on a weakened system, now frequently appears to be prevented by the precautionary use of antibiotics.

Credit for better health and longer life must be given to a combination of factors. Improved sanitation, immunization programs, and better nutrition have combined with scientific advances in medication (such as antibiotics and sulfa drugs) to provide longer and healthier lives. The reduced outbreaks of food- and water-borne diseases attest to the general betterment of health conditions. In 1938 outbreaks of such diseases totaled 36,507 cases in the United States; in 1951 only 11,244 cases were reported.[11]

[11] Building America's Health, vol. 3, The President's Commission on the Health Needs of the Nation, Washington, D. C., 1953, table 87, p. 72.

Principal infections and diseases which respond to antibiotic therapy

Bacterial infections which cause such diseases as pneumonia, mastoiditis, bacterial endocarditis (inflammation of the lining of the cavity of the heart, particularly of the valves), meningitis, peritonitis, typhoid fever, and some venereal diseases are susceptible to antibiotics. But viral infections, with 1 or 2 minor exceptions, resist antibiotics. This means that antibiotics are not effective against the microbes which cause such infections as the common cold, measles, infantile paralysis, influenza, mumps, rabies, shingles, smallpox, and yellow fever.

As new drugs, each of the antibiotic substances now on the market has proved its capacity for antimicrobial action to the satisfaction of the Food and Drug Administration. In use, the action of an antibiotic will vary according to the seriousness of the infection or disease, according to the patient's condition, and according to the size of the dosage. Often the same antibiotic is either bactericidal or bacteriostatic depending on the size of the dosage administered or on the vitality of the disease-causing micro-organism. (A *bactericidal* antibiotic is one which destroys the disease-causing bacterial micro-organism. A *bacteriostatic* antibiotic stops the growth of the disease-causing bacterial micro-organism.)

As stated above, for each antibiotic there are certain disease-causing micro-organisms against which the antibiotic is active (either as a growth inhibitor or as a killer). This spectrum of potency is not related to the number of diseases but rather to the kinds of disease-causing organisms that the antibiotic can harm in some way. In general terms, the major areas of effectiveness of important antibiotics can be summarized as follows. Penicillin has a high order of activity against most of the Gram-positive organisms, some of the Gram-negative bacteria,[12] various spirochetes, and the actinomyces. Other organisms such as the virus of lymphogranuloma venereum and psittacosis are less sensitive to penicillin.[13] The streptomycins are useful in treating tuberculosis and other infections.

Potency against a broader spectrum of organisms has been found in other antibiotics, such as chloramphenicol and the three tetracyclines. The tetracyclines are effective against most of the Gram-positive bacteria and a wide variety of Gram-negative organisms; they are highly effective against rickettsias and against some large viruses. They are also effective against organisms causing granuloma inguinale and trachoma, the actinomycetes, spirochetes, some protozoa and other parasites. Chloramphenicol has an antimicrobial spectrum

[12] Gram-positive and Gram-negative refer to the reaction of bacteria to a stain developed by Hans Christian Gram of Denmark.

[13] Allen E. Hussar and Howard L. Holley, Antibiotics and Antibiotics Therapy, The Macmillan Co., New York, 1954, p. 58.

similar to the tetracyclines, with some exceptions. The outstanding advantage of this antibiotic is its effectiveness against the typhoid organisms, not shared by other antibiotics.[14]

Because of the wider range of organisms reacting to chloramphenicol and the tetracyclines, they are commonly referred to as *broad spectrum* antibiotics. Penicillin, however, within its range of activity, is reported to be usually more potent than broad spectrum antibiotics.[15] Again, it is stated that within the penicillin range is to be found the greatest number of infections and diseases occurring in the Nation.[16]

Public health statistics

Records of the occurrence of major infections and diseases are maintained by the United States Department of Health, Education, and Welfare. These statistics reveal that the average duration of some illnesses is shortening, and that infectious diseases are taking smaller tolls each year. Part of this favorable showing is undoubtedly due to the effectiveness of antibiotics in the treatment of such diseases. Other important factors, as previously noted, are improved sanitation in food and water supplies, living quarters, refuse disposal, immunization programs, better nutrition, and scientific advances in medicine of which antibiotic therapy is only one part. Also, it should be noted that some of the diseases that have shown great decreases are not subject to effective treatment with antibiotics.

Statistics published by the United States Department of Health, Education, and Welfare (table 76) show the number of reported cases of specified diseases in the United States during the years 1946 to 1955, inclusive.

Diseases in which antibiotics are regarded as effective are indicated by asterisks in the table. Among these, diphtheria cases dropped from 16,354 in 1946 to 1,984 in 1955, and venereal diseases from 814,840 cases in 1946 to 371,361 in 1955. Bacillary dysentery dropped from 24,286 cases in 1946 to 13,912 cases in 1955. Tuberculosis dropped from 119,256 cases in 1946 to 98,737 cases in 1955.

Other diseases listed in the table, although not directly affected by antibiotics, are sometimes treated with them as a supportive or prophylactic measure. For instance, antibiotics may be administered in cases of measles, smallpox, sleeping sickness, etc., in order to forestall complications that sometime follow such diseases.

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[14] Ibid., pp. 115–116 and 144.

[15] Louis S. Goodman and Alfred Gilman, The Pharmacological Basis of Therapeutics, The Macmillan Co., New York, 1956, pp. 1322, 1323.

[16] Harrison F. Flippin and George M. Eisenberg, Antimicrobial Therapy in Medical Practice, F. A. Davis Co., Philadelphia, 1955, p. 12.

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TABLE 76.—*Reported cases of specified notifiable diseases, United States, 1946–55*

Disease	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955
Amebiasis*	4, 093	3, 365	4, 871	5, 543	4, 568	3, 550	4, 280	4, 444	3, 523	3, 348
Anthrax*	40	69	60	54	49	60	47	45	22	39
Botulism		44	39	24	20	33	18	18	18	16
Brucellosis (undulant fever)*	5, 887	6, 321	4, 991	4, 235	3, 510	3, 139	2, 537	2, 032	1, 823	1, 444
Dengue	40	35	24	46	26	16	5	8	6	1
Diphtheria*	16, 354	12, 262	9, 493	7, 969	5, 796	3, 983	2, 960	2, 355	2, 041	1, 984
Dysentery, bacillary (shigellosis)*	24, 286	17, 048	23, 753	29, 080	23, 367	32, 215	23, 197	16, 533	13, 846	13, 912
Encephalitis, acute infectious (sleeping sickness)	728	785	730	903	1, 135	1, 123	1, 912	1, 935	2, 606	2, 588
Hepatitis, infectious, and serum		1, 092	709	2, 027	2, 820	7, 349	17, 428	33, 700	50, 093	31, 961
Leprosy	43	56	63	41	44	57	57	60	56	75
Leptospirosis		14	18	17	30	9	62	42	48	24
Malaria	48, 610	15, 116	9, 606	4, 151	2, 184	5, 600	7, 023	1, 310	715	522
Measles	695, 843	222, 375	615, 104	625, 281	319, 124	530, 118	683, 077	449, 146	682, 720	555, 156
Meningococcal infections*	5, 693	3, 420	3, 376	3, 519	3, 788	4, 164	4, 884	5, 077	4, 436	3, 455
Plague*		1		3	3	1				
Poliomyelitis, acute	25, 698	10, 827	27, 726	42, 033	33, 300	28, 386	57, 879	35, 592	38, 476	28, 983
Psittacosis*	26	27	32	35	26	25	135	169	563	333
Q fever*			1	2		8	7	4	8	63
Rabies in man [1]	34	26	24	10	18	18	24	12	13	6
Rabies in animals [2]	10, 850	8, 920	8, 495	7, 587	7, 901	8, 008	8, 445	8, 903	7, 297	5, 799
Rocky Mountain spotted fever*	587	596	547	570	464	347	327	313	294	295
Salmonellosis, paratyphoid fever*	723	951	882	1, 243	1, 233	1, 773	2, 596	3, 946	5, 375	5, 447
Scarlet fever and streptococcal sore throat*	125, 511	93, 595	91, 295	87, 220	64, 494	84, 151	113, 677	132, 935	147, 785	147, 502
Smallpox [3]	337	176	57	49	39	11	21	4	9	2
Tetanus		560	601	579	486	506	484	506	524	462
Trachoma*		1, 540	2, 565	1, 475	1, 584	2, 916	3, 088	773	1, 172	1, 130
Trichiniasis		451	487	353	327	393	367	395	277	264
Tuberculosis, all forms*	119, 256	134, 946	137, 006	134, 865	121, 742	118, 491	109, 837	106, 925	100, 540	98, 737
Tularemia*	1, 355	1, 401	1, 086	1, 179	927	702	668	601	681	584
Typhoid fever*	3, 268	3, 075	2, 840	2, 795	2, 484	2, 128	2, 341	2, 252	2, 169	1, 704
Typhus fever, endemic (murine)* [4]	3, 365	2, 050	1, 171	985	685	378	205	221	163	135
Venereal diseases: [5]										
Gonorrhea*	415, 855	380, 666	345, 501	317, 950	286, 746	254, 057	253, 839	246, 311	249, 883	244, 279
Syphilis*	385, 524	355, 592	314, 313	256, 463	217, 558	174, 924	169, 198	150, 026	131, 260	123, 004
Other specified venereal diseases*	13, 461	14, 371	12, 559	11, 034	8, 187	6, 885	6, 093	5, 209	4, 650	4, 078
Whooping cough (pertussis)*	109, 860	156, 517	74, 715	69, 479	120, 718	68, 687	45, 030	37, 129	60, 886	62, 786

*Diseases which have been treated successfully by antibiotics.

[1] For 1946 to 1954, figures represent registered deaths.

[2] For 1946 to 1951, figures from Agricultural Research Service, U. S. Department of Agriculture.

[3] For 1954 to 1955, these cases do not fulfill the generally accepted criteria for a diagnosis of smallpox.

[4] Includes a few cases reported as Brill's disease.

[5] For 1946 to 1951, figures (civilian cases only) from the venereal disease program, Public Health Service.

Source: Department of Health, Education, and Welfare, Morbidity and Mortality Weekly Report, vol. 4, No. 53, Washington, D. C., Sept. 27, 1956, p. 3.

Table 77 summarizes the data shown in table 76 in such a way as to permit direct comparisons of the incidence of diseases against which the use of antibiotics is an effective treatment with that of all other diseases reported.

TABLE 77.—*Occurrences of reportable diseases: 1946–55*

Year	Total number reported [1]	Total occurrences of diseases against which antibiotics are effective [2]		Total occurrence of other diseases reported
		Number	Percent of total cases reported	
1946	2, 017, 327	1, 235, 144	61. 2	782, 183
1947	1, 448, 290	1, 187, 813	82. 0	260, 477
1948	1, 694, 740	1, 031, 057	60. 8	663, 683
1949	1, 618, 799	935, 698	57. 8	683, 101
1950	1, 235, 383	867, 929	70. 3	367, 454
1951	1, 344, 211	762, 584	56. 7	581, 627
1952	1, 521, 748	744, 946	49. 0	776, 802
1953	1, 248, 931	717, 300	57. 4	531, 631
1954	1, 513, 978	731, 120	48. 3	782, 858
1955	1, 340, 118	714, 259	53. 3	625, 859
Percent decrease: 1946–55	33. 6	42. 2		20. 0

[1] Summary of table 76, itemization of diseases reported.
[2] Summary of table 76, itemization of diseases which have been successfully treated by antibiotics.

Source: U. S. Department of Health, Education, and Welfare, Morbidity and Mortality Weekly Report, vol. 4, No. 53, Washington, D. C., Sept. 27, 1956, p. 3.

The showing is that among the diseases for which antibiotics are effective, the totals reported dropped from 1,235,144 in 1946 to 714,259 in 1955, a 42.2-percent drop. For all other diseases, for which antibiotics are not regarded as effective, the totals reported fell from 782,183 in 1946 to 625,859 in 1955, a 20-percent drop. The table also shows that the proportion of all diseases reported that were treatable with antibiotics fluctuated from year to year, but showed an overall drop from 61.2 percent of all diseases reported in 1946 to 53.3 percent in 1955. Notwithstanding the fact that not all of the decrease in number of diseases treatable with antibiotics is ascribable to such treatment, it appears that the use of antibiotics, early diagnosis, and other factors have limited the epidemic spread and thus the number of these diseases which occurred.

One fact shown by Census statistics is that during the years 1945–55, deaths have been reduced most sharply among young people, as shown by table 78, which shows the number of deaths per 1,000 population in different age brackets. The average annual deaths for all age groups were greater during the period before antibiotics than they were during the period since antibiotics (shown in the last column).

Here, again, the most that can be concluded is that the use of antibiotics has been one of a number of factors contributing to the de-

TABLE 78.—*Death rates by age groups, per 1,000 population, United States, 1900 to 1955*

Age	1900	1910	1920	1930	1940	1945	1950	1953	1954	1955	Average annual deaths for years shown	
											1900–45 (pre-antibiotics period)	1945–55 (post-antibiotics period)
Total	17.2	14.7	13.0	11.3	10.8	10.6	9.6	9.6	9.2	9.3	12.9	9.7
Under 1 year	162.4	131.8	92.3	69.0	54.9	42.5	33.0	31.4	30.3	29.6	92.2	33.4
1 to 4 years	19.8	14.0	9.9	5.6	2.9	2.0	1.4	1.3	1.2	1.2	9.0	1.4
5 to 14 years	3.9	2.9	2.6	1.7	1.0	.9	.6	.5	.5	.5	2.2	.6
15 to 24 years	5.9	4.5	4.9	3.3	2.0	1.9	1.3	1.2	1.1	1.2	3.8	1.3
25 to 34 years	8.2	6.5	6.8	4.7	3.1	2.7	1.8	1.6	1.5	1.5	5.3	1.8
35 to 44 years	10.2	9.0	8.1	6.8	5.2	4.6	3.6	3.3	3.1	3.1	7.3	3.5
45 to 54 years	15.0	13.7	12.2	12.2	10.6	9.6	8.5	8.1	7.7	7.5	12.2	8.3
55 to 64 years	27.2	26.2	23.6	24.0	22.2	20.5	19.0	18.4	17.4	17.4	24.0	18.5
65 to 74 years	56.4	55.6	52.5	51.4	48.4	42.6	41.0	40.2	39.0	39.4	51.2	40.4
75 to 84 years	123.3	122.2	118.9	112.7	112.0	98.4	93.3	92.5	87.6	89.1	114.6	92.2
85 and over	260.9	250.3	248.3	228.0	235.7	209.6	202.0	186.7	174.6	178.2	238.8	190.2

Source: U. S. Department of Commerce, Bureau of the Census, Statistical Abstract of the United States, 1956, Washington, D. C., p. 66.

creases in death rates that have occurred since 1945. In considering the showings for age groups, it is to be kept in mind that, according to the United States Department of Health, Education, and Welfare, 75 percent of all deaths in 1954 were attributable to the aging and birth processes, rather than to infections or contagions for which antibiotics might be expected to offer effective therapy. Included among these leading causes of death in 1954 were cardiovascular-renal diseases (54 percent of the death rate for all causes in 1954) and malignant neoplasms (16 percent). Six other causes, of which four may respond to treatment by antibiotics, accounted for most of the balance of the deaths.[17]

Statistics of the United States Department of Health, Education, and Welfare which confirm the general statement made above are presented in table 79, which shows the rates of deaths per 100,000 population from important causes. The names of eight diseases which have been treated successfully by antibiotics are followed by an asterick in the table. Thus the table contains the basic data for computing the relative decreases in death rates for eight diseases treatable with antibiotics for comparison with the rates for other diseases during the period from 1945 to 1955, inclusive. Antibiotics are, of course, effective in the treatment of many other diseases.

Eight of the most important diseases for which antibiotics offer effective therapy are tuberculosis, syphilis, dysentery, scarlet fever, diphtheria, whooping cough, meningococcal infections, and pneumonia. The total number of deaths for these diseases combined fell from 89.4 per 100,000 population in 1945 to 39.0 per 100,000 in 1955, a decrease of 50.4 death per 100,000 population. This is a 56.4-percent decrease. For all other causes of death, the total number fell from 968.7 per 100,000 in 1945 to 890.5 in 1955, a decrease of about 8.1 percent.

Among those diseases for which antibiotics offered a new therapy during the period, deaths from tuberculosis were 28.8 less per 100,000 population in 1955 than they were in 1945, a decrease of 75.2 percent. By comparison, the percentage decrease in number of deaths per 100,000 population during the preceding 10 years, 1936–45, was 28.6 percent.[18] There were 5.6 fewer deaths per 100,000 population from syphilis in 1955 than in 1945, a decrease of 70.9 percent as compared with a decline of 34.6 percent during the preceding 10 years, 1936–45. Pneumonia deaths decreased 11.4 per 100,000 population from 1945 to 1955, a decrease of 30.6 percent. These three diseases accounted for nearly 36 percent of the total decline in the death rates in the 10-year

[17] Department of Health, Education, and Welfare, Mortality From Selected Causes, vol. 44, No. 10, August 10, 1956, p. 201.

[18] Department of Health, Education, and Welfare, Vital Statistics Special Reports, 1936–53, vol. 43, No. 2, April 4, 1596, p. 24.

TABLE 79.—*Death rates for selected causes: United States, 1945–55*

[Per 100,000 population]

Cause of death	1945	1946	1947	1948	1949	1950	1951	1952	1953	1954	1955, estimated	Increase or decrease, 1945–55	Percent of total decrease, 1945–55
All causes	1,058.1	996.5	1,007.6	988.6	971.0	963.8	966.3	961.0	958.5	918.9	929.5	−128.6	100.00
Tuberculosis*	38.3	34.9	32.1	28.8	26.3	22.5	20.1	15.8	12.3	10.2	9.5	−28.8	22.4
Syphilis*	7.9	6.9	6.6	5.9	5.8	5.0	4.1	3.7	3.3	3.0	2.3	−5.6	4.4
Dysentery*	1.3	.7	.7	.8	1.0	.6	.7	.6	.6	.4	.3	−1.0	.8
Scarlet fever*	.9	.6	.4	.4	.3	.2	.2	.2	.2	.2	.1	−.8	.6
Diphtheria*	1.2	.9	.6	.4	.4	.3	.2	.1	.1	.1	.1	−1.1	.9
Whooping cough*	1.3	.9	1.4	.8	.5	.7	.6	.3	.2	.2	.3	−1.0	.8
Miningococcal infections*	1.3	.9	.6	.6	.6	.6	.7	.9	.8	.6	.6	−.7	.5
Acute Poliomyelitis	.9	1.3	.4	1.3	1.8	1.3	1.0	2.0	.9	.8	.6	−.3	.2
Measles	.2	.9	.3	.6	.6	.3	.4	.4	.3	.3	.2	0	-----
Other infective and parasitic diseases [1]	4.6	3.9	3.4	3.2	2.9	2.6	2.8	2.9	2.7	2.7	2.5	−2.1	1.6
Malignant neoplasms	134.9	131.0	133.5	136.2	138.8	139.8	140.5	143.3	144.7	145.6	147.6	+12.7	−9.8
Diseases of cardiovascular system	496.8	469.9	488.0	487.8	484.6	494.4	498.3	498.3	502.7	484.6	493.2	−3.6	2.8
Influenza	9.6	7.9	6.7	4.3	3.1	4.4	4.5	3.6	6.0	1.7	1.7	−7.9	6.1
Pneumonia*	37.2	32.4	32.0	29.8	26.9	26.9	26.9	26.1	27.0	23.8	25.8	−11.4	8.9
Accidents	6.83	66.3	65.8	63.6	60.6	60.6	62.5	61.7	60.0	55.9	55.6	−12.7	9.9
Suicides	11.2	11.6	11.6	11.2	11.4	11.4	10.4	10.0	10.1	10.1	9.9	−1.3	1.0
All other causes	242.2	225.5	223.5	212.9	205.4	192.2	192.4	191.1	186.6	178.7	179.2	−63.0	49.0

*Diseases and infections which have been successfully treated by antibiotics.
[1] Many of these diseases probably respond to antibiotics therapy.

Source: Department of Health, Education, and Welfare, Monthly Vital Statistics Report, vol. 4, No. 13, Washington, D. C., May 28, 1956, p. 7.

period, with tuberculosis alone accounting for over 22 percent of the decrease.[19] For the remaining 5 diseases, death rates from which were already low in 1945, the decreases in number of deaths per 100,000 were small, but nevertheless the percentage decreases were large.

By 1953, deaths from typhoid had been virtually eliminated.[20] Diphtheria, which in 1945 caused 1.2 deaths per 100,000 population, caused deaths at the rate of only 0.1 per 100,000 in 1955.[21] Deaths from dysentery and whooping cough have shown similar decreases.[22] In fact, deaths from these last two children's diseases are now limited almost entirely to infants under 1 year of age.

Most of the lives affected by antibiotics were apparently in the lower age brackets. Therefore the economic consequences of a saving of lives may be considered substantial. There is no way of isolating the exact contribution of antibiotics to public health. However, published data do reveal both fewer contagious diseases and lower death rates for the "antibiotics period" than for the period immediately preceding their use.

Time lost through illness

Whether or not antibiotics have shortened the duration of illnesses is difficult to prove statistically. While many studies have been made of illnesses and the loss of earning power attributed to them, these studies do not compare data on a year-to-year basis, and therefore cannot be used to compare the preantibiotics period with the years since 1945. In any case, measurements of the length or even the occurrences of illness are inexact since each individual has a different threshold of tolerance. One will be bedridden with a slight cold; another will remain on the job even though seriously ill.

The Public Health Service has made a number of illness surveys in the past 25 years.[23] These surveys do not, however, disclose trends in illnesses or trends in time lost through illnesses from year to year. Therefore, the effect of antibiotics on length or occurrences of illnesses is not observable from these surveys.

However, hospital records do provide some insight into the periods preceding and following the introduction of antibiotics. It has been reported that the average length of stay in general hospitals was reduced from 14 days per patient in 1935 to 9.3 days in 1953.[24] Another

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[19] Department of Health, Education, and Welfare, Monthly Vital Statistics Report, vol. 4, No. 13, May 28, 1956, p. 7.

[20] Department of Health, Education, and Welfare, Vital Statistics Special Reports, vol. 43, No. 4, May 16, 1956, p. 56.

[21] Ibid., No. 6, May 18, 1956, p. 88.

[22] Ibid., No. 5, May 17, 1956, p. 72; vol. 43, No. 7, May 21, 1956, p. 104.

[23] Department of Health, Education, and Welfare, "Sickness Experience in Selected Areas of the United States," Public Health Monograph No. 25, Washington, 1955.

[24] The Chemical Industry Facts Book, Manufacturing Chemists' Association, Inc., Washington, 1953, p. 80.

J. Frederic Dewhurst, America's Needs and Resources: A New Survey, Twentieth Century Fund, New York, 1955, p. 310.

report, covering the length of stay in all general and special short-term hospitals, discloses that the average number of days was reduced from 9.1 days in 1946 to 7.9 days in 1953.[25]

With reduction in the incidence of tuberculosis, the number of hospital beds maintained for this disease was reduced 3.5 percent in 1953 over the prestreptomycin year of 1946. While streptomycin therapy has undoubtedly contributed to the improved tuberculosis picture, other data on the length of stay in hospitals for other diseases are less conclusive as a measure of the effects of treatment with antibiotics on time lost from other diseases.

Some interpretations of public health data

Between 1945 and 1955 there was a decline of 50.4 deaths per 100,000 from diseases that respond to antibiotic treatment (calculated from table 79). On the basis of the 1955 population, this would amount to 83,000 lives. Other factors, however, such as an improved economic and social status of the population and better health facilities and practices, have contributed substantially to reducing deaths from these diseases, as well as from others.

The fact that the average patient spends a shorter period in the hospital than formerly reflects a change in medical science and therapy. An important part of the new therapy is the use of antibiotics. The result is an earlier return to normal life and work for those diseases that yield to antibiotic treatments. In the case of industrial accidents also, where antibiotics have the same unique value that they had for war wounds, both the lives saved and the sicktime saved represent both actual and potential increase in productivity. However, there is no way to measure exactly the contribution of antibiotics to the improved public health situation, or the cumulative effects of that improvement on national productivity.

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[25] American Hospital Association, "Hospitals," Administrators Guide Issue, vol. 28, No. 6, pt. II, June 1954, p. 16.

APPENDIX I

FTC Data Requests

Exhibit 1—FTC Data Request, 1956

Federal Trade Commission

Washington 25

OFFICE OF THE SECRETARY

Gentlemen: The Federal Trade Commission, in the exercise of the powers vested in it by section 6 of the Federal Trade Commission Act, and pursuant to a resolution adopted and entered of record, has authorized and directed the collection of reports from corporations engaged in commerce in antibiotic substances.

In this connection, and pursuant to the powers conferred upon it by law, the Commission hereby requires you to file with it within 20 days after receipt of this order a report containing the information described in the attached report request and instructions relating thereto.

By direction of the Commission.

Robert M. Parrish,
(S) Robert M. Parrish,
Secretary.

Federal Trade Commission

AMENDED RESOLUTION—REPORT ON ANTIBIOTIC DRUG INDUSTRY

Whereas the commercial manufacture of antibiotic substances in the United States has within less than a decade, developed into one of the major branches of the ethical drug industry, and has come to be an important source of newly discovered food and feed supplements; and

Whereas the general public contributed largely to the establishment of an antibiotics industry in the United States through Federal Government promotion of research by which methods of producing antibiotics were developed, and through Government incentives to stimulate commercial production of penicillin; and

Whereas the industry is important to the public health and welfare, since antibiotic substances are more potent against a variety of diseases than any drugs previously known, and other substances produced by antibiotic manufacturers have unique value as food and feed supplements in human and animal nutrition, while new potentialities are still being revealed; and

Whereas there is a broad public interest in the availability at reasonable prices of the antibiotic drugs, as well as in continuing research and continuing incentives for the discovery and development of new uses and new antibiotics under the private enterprise system; and

Whereas it appears to the Commission that, for the reasons stated herein, and for the purposes set forth in section 6 of the Federal Trade Commission Act, an investigation of the antibiotics industry by the Federal Trade Commission would be in the public interest: Now, therefore, be it

Resolved, That the Commission, in the exercise of the powers vested in it by sections 6 and 9 of the Federal Trade Commission Act, and with the aid of any and all powers conferred upon it by law and any and all compulsory processes available to it, do forthwith proceed to investigate, for the reasons and purposes stated herein, the organization, business, conduct, practices, and management of corporations engaged in the production, sale or distribution of antibiotic drugs in commerce, as commerce is defined in the Federal Trade Commission Act, and the relations of these corporations to each other and to other corporations, and to individuals, associations, and partnerships.

By direction of the Commission.

(S) Robert M. Parrish,
ROBERT M. PARRISH,
Secretary.

JULY 13, 1956.

Budget Bureau No. 56–5601
Approval expires Nov. 30, 1956

FEDERAL TRADE COMMISSION

Washington 25

This report is required by law. It is mandatory under authority of the Federal Trade Commission Act.

Not later than August 13, 1956, send one copy of this report to the Federal Trade Commission, Bureau of Economics, Washington 25, D. C.

Each report should be certified to as follows:

Certification

I, the undersigned, president (or vice president, or other principal officer) of the company for which this report is made, declare that this report (including any accompanying exhibits) has been examined by me and is, to the best of my knowledge and belief, a true report, made in good faith.

----------------------------------	----------------------------------
(Signature)	(Print name and title)
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(Name and address of reporting company)	(Month, day, year)

NOTES

1. The Commission reserves the right under section 6 (f) of the Federal Trade Commission Act to make public from time to time such portions of the information obtained by it, except trade secrets and names of customers, as it shall deem expedient in the public interest.
2. The Federal Trade Commission is informed that frequently corrections are made in the data on production and sales after they have been submitted to the Tariff Commission, either by the Commission or by the companies. In all cases the interest of the Federal Trade Commission is in receiving the latest, corrected data.
3. This report request is being sent to parent companies. A separate report is requested for each reporting corporate entity on the same basis as called for by the Tariff Commission.
4. List the corporate entities included in the answer to each question.

DATA SCHEDULES

I. PRODUCTION AND SALES OF ANTIBIOTICS AND OF VITAMIN B_{12}, 1948–55

Submit the information on production and sales of antibiotics and of vitamin B_{12}, as called for in each of the following Tariff Commission schedules (wherever not applicable, so state).

Synthetic Organic Chemicals:

Production and Sales in 1948, Section X.
Production and Sales in 1949, Section X.
Production and Sales in 1950, Section X.
Production and Sales in 1951, Section VI.
Production and Sales in 1952, Section VI.
Production and Sales in 1953, Section VI.
Production and Sales in 1954, Section VI.
Production and Sales in 1955, Section VI.

Instructions

A. If you have become an original manufacturer of antibiotics and/or of vitamin B_{12} since January 1, 1948, through acquisition of another company, submit copies of the following reports requested by the United States Tariff Commission on production and sales of antibiotics and vitamin B_{12}: (i) your reports subsequent to the acquisition, (ii) the earlier reports of the acquired company or companies, and (iii) the reports of any companies of which the company or companies acquired by you was the acquirer.

B. If you have not yet submitted to the Tariff Commission your report on production and sales of antibiotics and of vitamins in 1955, data for that year should nevertheless be supplied along with similar information for earlier years. Follow the Tariff Commission's schedule contained in section VI of "Synthetic Organic Chemicals, Production and Sales in 1955" for reporting production and sales of antibiotics and of vitamin B_{12}.

C. The reporting requirement will be satisfied if you furnish directly to the Federal Trade Commission a copy of the report (as corrected) which you sent to the Tariff Commission. If you prefer that the Federal Trade Commission obtain from the Tariff Commission data you submitted to the latter covering antibiotics and vitamin B_{12}, complete and send to the Tariff Commission the attached letter on your own letterhead and also send a copy to the Federal Trade Commission. This letter will authorize the Tariff Commission to release the data to the Federal Trade Commission. The Tariff Commission does not release to other Federal agencies individual company data accepted in confidence unless it has been authorized to do so.

II. PRICES

A. Submit a complete chronological record of the prices (including established or suggested prices, retail or other) of each of the principal dosage forms of every antibiotic and vitamin B_{12} sold or offered for sale by you from January 1, 1948, through December 31, 1955, together with applicable schedules of discounts, allowances and all other terms and conditions of sale.

B. Submit a complete chronological record of the bulk prices of each antibiotic and vitamin B_{12} sold or offered for sale by you in bulk from January 1, 1948, through December 31, 1955, together with applicable schedules of discounts, allowances and all other terms and conditions of sale.

Instructions

If, since January 1, 1948, you have acquired or merged with a corporation which was not producing antibiotics (that is, which was not an "original manufacturer" in the Tariff Commission's sense), price information on the antibiotics and vitamin B_{12} sold or offered for sale by that corporation during the years prior to its acquisition by you need not be reported at this time.

III. PATENTS

A. Submit a list of all patents, domestic and foreign (indicate country), owned or controlled by you and in any way related to antibiotics, grouping these patents as far as possible by particular antibiotics. Submit the following information for each such patent:

1. Number and date of issue (if not granted state patent pending).
2. Patentee or patentees.
3. Subject of invention (stated no more briefly than in *Index of Patents*).
4. How acquired (if by assignment, state relationship to you, as of date of assignment, of assignor or assignors).
5. Copies of any agreements entered into in connection with the settlement of interference proceedings instituted by the Patent Office, in consequence of which you were the successful applicant for the patent.
6. Copies of all license agreements, without regard to their dates and regardless of whether the licensor was your company or a predecessor in interest.
7. Royalty income, by each year owned.
8. Years during which patent was worked (used) by you.

B. Submit a list of all patents, domestic and foreign (indicate country), in any way relating to antibiotics, under which you have at any time been licensed or are now licensed, grouping these patents as far as possible by particular antibiotics.

Submit the following information for each such patent:

1. Number and date of issue.
2. Patentee or patentees.
3. Subject of invention (stated no more briefly than in *Index of Patents*).
4. Royalty payments by years, from date of license through 1955.

Instructions

If a patent is or can be used in the production of more than one antibiotic, list it by number in each appropriate place but give details only when the patent in question is first listed. A cross-reference will suffice thereafter.

(If you elect to use it, the following letter is to be mailed to the Tariff Commission and a copy thereof, on your business leaderhead, is to be mailed to the Federal Trade Commission, Bureau of Economics, Washington 25, D. C.)

United States Tariff Commission

Washington 25, D. C.

Gentlemen: You are hereby authorized to release to the Federal Trade Commission, Washington, D. C., the information on our production and sales of all antibiotics and of vitamin B_{12} which we reported to the Tariff Commission for use in connection with its reports on Synthetic Organic Chemicals, Production and Sales, for the following years.

☐ 1948	☐ 1952
☐ 1949	☐ 1953
☐ 1950	☐ 1954
☐ 1951	☐ 1955

In authorizing release of our reports to the Federal Trade Commission, we are aware of the fact that the Federal Trade Commission reserves the right under section 6 (f) of the Federal Trade Commission Act to make public from time to time such portions of the information obtained by it, except trade secrets and names of customers, as it shall deem expedient in the public interest.

Exhibit 2—FTC Data Request, 1957

Federal Trade Commission

Washington 25, D. C.

OFFICE OF THE SECRETARY

Gentlemen: The Federal Trade Commission, in the exercise of the powers vested in it by section 6 of the Federal Trade Commission Act, and pursuant to a resolution adopted and entered of record, has authorized and directed the collection of reports from corporations engaged in commerce in antibiotic substances.

In this connection, and pursuant to the powers conferred upon it by law, the Commission hereby requires you to file with it not later than July 1, 1957, a report containing the information described in the attached report request and instructions relating thereto.

By direction of the Commission.

Robert M. Parrish,
Secretary.

Approval expires Sept. 30, 1957
Budget Bureau No. 56–5701

Federal Trade Commission

Washington 25, D. C.

Antibiotics Manufacturing Industry Survey

This report is required by law. It is mandatory under authority of the Federal Trade Commission Act.

Not later than July 1, 1957, send one copy of this report to the Federal Trade Commission, Bureau of Economics, Washington 25, D. C.

Each report should be certified as follows:

Certification

I, the undersigned, president (or vice president, or other principal officer) of the company for which this report is made, declare that this report (including any accompanying exhibits) has been examined by me and is, to the best of my knowledge and belief, a true report, made in good faith.

----------------------------------	----------------------------------
(Signature)	(Print name and title)
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(Name and address of reporting company)	(Month, day, year)

General Statement

At this stage of the Federal Trade Commission's survey of the antibiotics industry, additional information is needed to supplement that already gathered from the industry and other sources.

A series of industry conferences has developed that—

1. Some of the information required is available from accounting and statistical records and can be reported without difficulty.
2. Some of the information needed can be readily estimated from operating records.
3. Some of the information may be available only as descriptive and analytical statements.
4. Some of the information is obtainable only by detailed analyses of inactive records and the consumption of an inordinate amount of time.
5. Some of the information may be unavailable.

If the information called for herein is not available, a statement must be submitted indicating whether records have never been kept or have been lost or destroyed. If the information is obtainable but an inordinate amount of time would be consumed in preparation, an explanation to this effect is required. Such explanation should be accompanied by an estimate of the time considered necessary to assemble the information. Inasmuch as the substance of these explanations as to why certain information is not provided is to be made a part of our report, all such statements submitted, as well as estimates of time requirements, should be set forth in a letter to the Commission and signed by a principal officer of the corporation.

Reference to schedule numbers should be made in response to schedules IV through XIII, and each of such schedules should be started on a separate page.

The Commission reserves the right under section 6 (f) of the Federal Trade Commission Act to make public from time to time such portions of the information obtained by it, except trade secrets and names of customers, as it shall deem expedient in the public interest.

Instructions for Schedules I, II, and III

Schedule I

Report in schedule I the operation of the departments, divisions, or subsidiaries of your company that are engaged in any way in the domestic production, finishing, compounding, packaging, and sales of antibiotics. In the column captioned "Total" report the total operations, including antibiotics, of this segment of your business. In column captioned "Antibiotics" report the data relating to the domestic production and sale of all products containing antibiotics. Where the accounting practices of your company do not normally provide a breakdown between antibiotic products and other products make such allocations as in your judgment will most accurately reflect the results of operations. Indicate bases of allocation.

Line 1.—Include in net sales all domestic sales of antibiotics and antibiotic products and all export sales from domestic production. The export sales, if made to an exporter, should be included at the price received. If exports are transferred to another division for export or transferred directly to a foreign branch they should be included at approximate market price as though they were sales to exporters. Sales should be reported net of all returns, allowances and trade discounts.

Line 4—Production costs.—Include here all costs that you usually consider to be production costs including that part of the research and development costs considered to be part of production. If amortization of emergency facilities or other accelerated depreciation is included, such amounts are to be shown at the bottom of the schedule.

Schedule II

Schedule II calls for a breakdown of the data reported under the "Antibiotics" column of schedule I.

A separate sheet should be prepared for each antibiotic manufactured and/or sold. With respect to the various types of penicillin, a separate sheet should be completed for each of the following:

Potassium penicillin.
Procaine penicillin.
Benzathine penicillin.
Penicillin V.
Combination of potassium and procaine penicillin.
All other penicillins or combinations of penicillins.

All formulations and products containing two or more antibiotics, except for those combinations covered above, are to be grouped together in one schedule for reporting purposes. Streptoduocin should also be reported on a separate schedule II. Additional copies of schedule II are available upon request.

Where the accounting practices of your company do not normally provide a breakdown between antibiotics, make such allocations as in your judgment will most accurately reflect results of operations. Indicate the bases of the allocations.

Line 1—Net sales—bulk antibiotic.—Include here all sales of the antibiotic in the bulk form.

Line 2—Net sales—packaged products under own labels.—Include all sales of the antibiotic in dosage forms and formulations, except animal feed supplements, made under your own labels and trademarks.

Line 3—Net sales—other packaged products.—Include here all sales of the antibiotic in dosage forms and formulations, except animal feed supplements, made under the labels of others or unlabeled.

Line 4—Animal feed supplements.—Include here all sales of animal feed supplements containing the antibiotic.

Line 5—Total net sales—total of lines 1 through 4.—Sales should be reported net of all returns, allowances, and trade discounts. Export sales should be included on the basis outlined in instructions for schedule I, line 1.

Line 9—Research and development.—Report here only the research and development related to production, such as research to improve production methods.

Line 19—Bulk antibiotic sold.—Report here the cost of the sales reported in line 1.

Line 20—Bulk transferred for use in other products.—Report here the cost of the bulk antibiotic transferred, e. g., bulk used in products containing more than one antibiotic, the sales and costs of which are reported on another schedule II.

Line 38—Research and development expenses.—Include research and development expense chargeable directly to the antibiotic and also the share of general research allocated to this antibiotic.

Line 42—Other expenses.—Report here any items of cost or expense identifiable with or allocated to the antibiotics which have not been included elsewhere in the schedule.

Schedule III

Schedule III should report the assets of that segment of your business for which income and expense are reported in schedule I. For these assets used only in part for antibiotics make such allocations as in your judgment will most accurately reflect the investment in antibiotics facilities. Furnish the bases of allocation.

Budget Bureau No. 56-5701

Approval expires September 30, 1957

SCHEDULE I - COMPARATIVE STATEMENT OF INCOME AND EXPENSE

Years ending December 31 or Fiscal Years ending ____________

____________ (Name of Company)

____________ (Address)

	1950		1951		1952	
	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total
1 Net Sales						
Cost of Goods Sold:						
2 Finished Goods Opening Inventory						
3 Purchases for Resale						
4 Production Costs						
5 Total Goods Available (Total of lines 2, 3, and 4)						
6 Less Finished Goods Closing Inventory						
7 Cost of Goods Sold (Line 5 less line 6)						
8 Gross Profit on Sales (Line 1 less line 7)						
Selling, General and Administrative Expenses:						
9 Salesmen's and Detailmen's Compensation and Expenses						
10 Other Selling Expenses						
Advertising and Promotion:						
11 Samples						
12 Direct Mail						
13 Periodicals (Including Journals)						
14 Other (Specify)						
15						
16						
Research and Development Expenses: (Give details in Schedule IA)						
17 Chargeable Directly to Products or Lines						
18 Other Research						
19 Administrative Expenses						
20 Other Expenses (Identify major items)						
21						
22						
23 Total Selling, General and Administrative Expenses (Total of lines 9 thru 22)						
24 Net Operating Profit before Income from Royalties and Licenses (Line 7 less line 23)						
25 Income from Royalties and Licenses - Domestic sources						
26 Income from Royalties and Licenses - Foreign sources						
27 Net Operating Income (Line 24 plus lines 25 and 26)						
28 Other Income or Deductions, Net (List Significant Items Below)						
29 Net Income before Federal Income and Excess Profits Taxes (Line 27 plus or minus line 28)						
30 Federal Income and Excess Profits Taxes						
31 Net Income After Taxes (Line 29 less line 30)						
32 Amount of Accelerated Amortization of Emergency Facilities under Certificates of Necessity						
33 Amount of Export Sales Included in Line 1						

Budget Bureau No. 56-5701

Approval expires September 30, 1957

SCHEDULE I - COMPARATIVE STATEMENT OF INCOME AND EXPENSE

Years ending December 31 or Fiscal Years ending ______

______ (Name of Company)

______ (Address)

	1953		1954		1955		1956	
	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total
1 Net Sales								
Cost of Goods Sold:								
2 Finished Goods Opening Inventory								
3 Purchases for Resale								
4 Production Costs								
5 Total Goods Available (Total of lines 2, 3, and 4)								
6 Less Finished Goods Closing Inventory								
7 Cost of Goods Sold (Line 5 less line 6)								
8 Gross Profit on Sales (Line 1 less line 7)								
Selling, General and Administrative Expenses:								
9 Salesmen's and Detailmen's Compensation and Expenses								
10 Other Selling Expenses								
Advertising and Promotion:								
11 Samples								
12 Direct Mail								
13 Periodicals (Including Journals)								
14 Other (Specify)								
15								
16								
Research and Development Expenses: (Give details in Schedule IA)								
17 Chargeable Directly to Products or Lines								
18 Other Research								
19 Administrative Expenses								
20 Other Expenses (Identify major items)								
21								
22								
23 Total Selling, General and Administrative Expenses (Total of lines 9 thru 22)								
24 Net Operating Profit before Income from Royalties and Licenses (Line 7 less line 23)								
25 Income from Royalties and Licenses - Domestic sources								
26 Income from Royalties and Licenses - Foreign sources								
27 Net Operating Income (Line 24 plus lines 25 and 26)								
28 Other Income or Deductions, Net (List Significant Items Below)								
29 Net Income before Federal Income and Excess Profits Taxes (Line 27 plus or minus line 28)								
30 Federal Income and Excess Profits Taxes								
31 Net Income After Taxes (Line 29 less line 30)								
32 Amount of Accelerated Amortization of Emergency Facilities under Certificates of Necessity								
33 Amount of Export Sales Included in Line 1								

Budget Bureau No. 56-5701

Approval expires September 30, 1957

SCHEDULE 1A - RESEARCH AND DEVELOPMENT EXPENSES

Years ending December 31 or Fiscal Years ending ____________

____
(Name of Company)

____
(Address)

Detail below the principal categories of research and development expenses	1950		1951		1952		1953		1954		1955		1956	
	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total

Budget Bureau No. 56-5701

Approval expires September 30, 1957

SCHEDULE II - COMPARATIVE STATEMENT OF INCOME AND EXPENSES

Years ending December 31 or Fiscal Years ending ____________

____________ (Name of Company)

____________ (Address)

	1950		1951		1952		1953	
	No. of Units	Amount	No. of Units	Amount	No. of Units	Amount	No. of Units	Amount
1 Net Sales - Bulk Antibiotics								
2 Net Sales - Packaged Products Under Own Labels								
3 Net Sales - Other Packaged Products								
4 Net Sales - Animal Feed Supplements								
5 Total Net Sales (Total of lines 1 thru 4)								
Cost of Goods Sold:								
6 Finished Goods Opening Inventory								
Production Costs:								
7 Raw Materials for Bulk Production								
8 Labor for Bulk Production								
9 Research and Development								
10 Royalties and Licenses								
11 Overhead for Bulk Production								
12 Credit for By-Products								
13 Cost of Bulk Production (Total of lines 7 thru 11 less line 12)								
14 Add Bulk Opening Inventory								
15 Purchases of Bulk Antibiotics								
16 Total Bulk Antibiotic Available (Total of lines 13, 14 and 15)								
17 Less Bulk Closing Inventory								
18 Bulk Antibiotic Used or Sold (Line 16 less 17)								
19 Bulk Antibiotic Sold								
20 Bulk Transferred for Use in Other Products								
21 Bulk Used in Production of Pkg. Prod. & Animal Feed Supp. (18 less 19 & 20)								
22 Other Materials of Own Manufacture								
23 Purchased Materials								
24 Containers and Packaging Materials								
25 Compounding and Packaging Labor								
26 Royalties and Licenses								
27 Compounding and Packaging Overhead								
28 Total Production Cost of Finished Goods (Total of lines 21 thru 27)								
29 Purchases for Resale								
30 Total Finished Goods Available for Sale (Line 28 plus line 29)								
31 Less Finished Goods Closing Inventory								
32 Cost of Finished Goods Sold (Line 30 less line 31)								
33 Total Cost of Goods Sold (Line 19 plus line 32)								
34 Gross Profit on Sales (Line 5 less line 33)								
Selling, General and Administrative Expenses:								
35 Salesmen's and Detailmen's Compensation and Expenses								
36 Other Selling Expenses								
37 Advertising Expenses								
38 Research and Development Expense								
39 Administrative Expense								
40 Other Expenses								
41 Total Selling, General and Administrative Expenses (Total of lines 35 thru 40)								
42 Other Expenses (Identify Major Items)								
43								
44 Income from Royalties and Licenses - Domestic sources								
45 Income from Royalties and Licenses - Foreign sources								
46 Amount of Export Sales Included in Line 5								
NOTE: Indicate the estimated amount expended for research and development of this antibiotic prior to its being marketed. $____________								

Budget Bureau No. 56-5701

Approval expires September 30, 1957

SCHEDULE II - COMPARATIVE STATEMENT OF INCOME AND EXPENSES

Years ending December 31 or Fiscal Years ending ____________

____________ (Name of Company)

____________ (Address)

		1954		1955		1956	
		No. of Units	Amount	No. of Units	Amount	No. of Units	Amount
1	Net Sales - Bulk Antibiotics						
2	Net Sales - Packaged Products Under Own Labels						
3	Net Sales - Other Packaged Products						
4	Net Sales - Animal Feed Supplements						
5	Total Net Sales (Total of lines 1 thru 4)						
	Cost of Goods Sold:						
6	Finished Goods Opening Inventory						
	Production Costs:						
7	Raw Materials for Bulk Production						
8	Labor for Bulk Production						
9	Research and Development						
10	Royalties and Licenses						
11	Overhead for Bulk Production						
12	Credit for By-Products						
13	Cost of Bulk Production (Total of lines 7 thru 11 less line 12)						
14	Add Bulk Opening Inventory						
15	Purchases of Bulk Antibiotics						
16	Total Bulk Antibiotic Available (Total of lines 13, 14 and 15)						
17	Less Bulk Closing Inventory						
18	Bulk Antibiotic Used or Sold (Line 16 less 17)						
19	Bulk Antibiotic Sold						
20	Bulk Transferred for Use in Other Products						
21	Bulk Used in Production of Pkg. Prod. & Animal Feed Supp. (18 less 19 & 20)						
22	Other Materials of Own Manufacture						
23	Purchased Materials						
24	Containers and Packaging Materials						
25	Compounding and Packaging Labor						
26	Royalties and Licenses						
27	Compounding and Packaging Overhead						
28	Total Production Cost of Finished Goods (Total of lines 21 thru 27)						
29	Purchases for Resale						
30	Total Finished Goods Available for Sale (Line 28 plus line 29)						
31	Less Finished Goods Closing Inventory						
32	Cost of Finished Goods Sold (Line 30 less line 31)						
33	Total Cost of Goods Sold (Line 19 plus line 32)						
34	Gross Profit on Sales (Line 5 less line 33)						
	Selling, General and Administrative Expenses:						
35	Salesmen's and Detailmen's Compensation and Expenses						
36	Other Selling Expenses						
37	Advertising Expenses						
38	Research and Development Expense						
39	Administrative Expense						
40	Other Expenses						
41	Total Selling, General and Administrative Expenses (Total of lines 35 thru 40)						
42	Other Expenses (Identify Major Items)						
43							
44	Income from Royalties and Licenses - Domestic sources						
45	Income from Royalties and Licenses - Foreign sources						
46	Amount of Export Sales Included in Line 5						
	NOTE: Indicate the estimated amount expended for research and development of this antibiotic prior to its being marketed. $ ____________						

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SCHEDULE III - COMPARATIVE STATEMENT OF ASSETS

Years ending December 31 or Fiscal Years ending__________

__________ (Name of Company)

__________ (Address)

	1950		1951		1952		1953		1954		1955		1956	
	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total	Antibiotics	Total
1 Current Assets														
Plants and Equipment:														
Devoted Wholly or Principally to Antibiotics:														
2 Land														
3 Buildings and Equipment														
4 Less Reserve for Depreciation														
Used Only in Part for Antibiotics:														
5 Land														
6 Buildings and Equipment														
7 Less Reserve for Depreciation														
8 Total Plants and Equipment														
9 Other Assets (Specify)														
10														
11 Total Assets														

Schedule IV

A. PRODUCTION AND SALES OF ANTIBIOTICS, 1943–47

(1) Supply the information on production and sales of antibiotics as submitted in each of the following Tariff Commission schedules (wherever not applicable so state):

Synthetic Organic Chemicals:
- Production and Sales in 1943, Section IX.
- Production and Sales in 1944, Section X.
- Production and Sales in 1945, Section X.
- Production and Sales in 1946, Section X.
- Production and Sales in 1947, Section X.

(2) For each of the years listed in (1), above, submit for each antibiotic for which production was reported, the quantity and value of interplant transfers (if there were none, so state).

B. PRODUCTION AND SALES OF ANTIBIOTICS AND VITAMIN B_{12}, 1956

Submit the information on production and sales of antibiotics and vitamin B_{12} as called for in the following Tariff Commission schedule (if not applicable, so state):

Synthetic Organic Chemicals, Production and Sales in 1956, Section VI.

C. PERIODS OF PRODUCTION

If you were once an "original manufacturer" (in the Tariff Commission's sense) of any antibiotic the production of which you discontinued at any time and which you were not producing on December 31, 1956, (1) indicate the periods during which each such antibiotic was produced, and (2) in the case of each discontinuance of production of any antibiotic, state the reason for discontinuing production.

Special Instructions for Schedule IV

"Any antibiotic" includes each penicillin salt (after the different salts began to be separately reported), as well as all antibiotics other than penicillin.

If you have become an original manufacturer of antibiotics and/or of vitamin B_{12} since January 1, 1943, through acquisition of another company, submit copies of the following reports requested by the United States Tariff Commission on production and sales of antibiotics and vitamin B_{12}: (1) your reports subsequent to the acquisition, (2) the earlier reports of the acquired company or companies, and (3) the reports of any companies of which the company or companies acquired by you was the acquirer.

If you have not yet submitted to the Tariff Commission your report on production and sales of antibiotics and of vitamin B_{12} in 1956, data for that year should be supplied to us along with the information requested for earlier years. Follow the Tariff Commission's schedule contained in Section VI of "Synthetic Organic Chemicals Production and Sales in 1956" for reporting production and sales of antibiotics and of vitamin B_{12}.

The reporting requirement will be satisfied if you supply directly to the Federal Trade Commission a copy of the report (as corrected) which you sent to the Tariff Commission. If you prefer that the Federal Trade Commission obtain from the Tariff Commission data you submitted to the latter covering antibiotics and vitamin B_{12}, complete and send to the Tariff Commission the attached

letter on your own letterhead and also send a copy to the Federal Trade Commission. This letter will authorize the Tariff Commission to release the data to the Federal Trade Commission. The Tariff Commission does not release to other Federal agencies individual company data accepted in confidence unless it has been authorized to do so.

(If you elect to use it, the following letter is to be mailed to the Tariff Commission and a copy thereof, on your business letterhead, is to be mailed to the Federal Trade Commission, Bureau of Economics. Washington 25, D. C.).

UNITED STATES TARIFF COMMISSION

Washington 25, D. C.

GENTLEMEN: You are hereby authorized to release to the Federal Trade Commission, Washington, D. C., the information on our production and sales of all antibiotics and of vitamin B_{12} which we reported to the Tariff Commission for use in connection with its reports on "Synthetic Organic Chemicals, Production and Sales," for the following years:

☐ 1943	☐ 1946
☐ 1944	☐ 1947
☐ 1945	☐ 1956

In authorizing release of our reports to the Federal Trade Commission, we are aware of the fact that the Federal Trade Commission reserves the right under section 6 (f) of the Federal Trade Commission Act to make public from time to time such portions of the information obtained by it, except trade secrets and names of customers, as it shall deem expedient in the public interest.

SCHEDULE V

PRICES

A. Submit a complete chronological record of the prices (including established or suggested prices, retail or other) of each of the principal dosage forms of every antibiotic and of vitamin B_{12} sold or offered for sale by you from January 1, 1943, through December 31, 1947, and during the calendar year 1956, together with applicable schedules of discounts, allowances, and all other terms and conditions of sale.

B. Submit a complete chronological record of the bulk prices of each antibiotic and of vitamin B_{12} sold or offered for sale by you in bulk from January 1, 1943, through December 31, 1947, and during the calendar year 1956, together with applicable schedules for discounts, allowances, and all other terms and conditions of sale.

NOTE.—If, between January 1, 1943, and December 31, 1956, you acquired, acquired control of, or merged with, a corporation which was not producing antibiotics (that is, which was not an "original manufacturer" in the Tariff Commission's sense), price information on the antibiotics nad vitamin B_{12} sold or offered for sale by that corporation during the years prior to your acquisition of its control, its acquisition by you, or its merger with you, need not be reported.

SCHEDULE VI

LOCATION OF PLANTS

State the location of each of your domestic and foreign antibiotic facilities as of December 31, 1950, and December 31, 1956, and indicate in each case the operations performed; i. e., manufacturing, processing, packaging, labeling.

Schedule VII

EXPENDITURES FOR NEW PLANT AND EQUIPMENT

Report for each calendar year from 1943 to 1956, inclusive, capital expenditures for domestic antibiotics plant and equipment as follows:

1. New construction (buildings and other structures).
2. Additions and alterations (to buildings and structures).
3. New equipment installed in both old and new buildings.

In instances of multiple use, provide estimates of expenditures for the portions used in antibiotics operations.

Schedule VIII

CONSTRUCTION FOR NATIONAL DEFENSE

A. For the period 1943–45, inclusive, supply the following information (when applicable) with respect to each antibiotics facility constructed or financed either by you, by an entity subsequently acquired by you, or by the Government, and operated by you or by an entity subsequently acquired by you.

1. Plancor No.
2. Certificate of Necessity No.
3. Location of facility.
4. Total cost of authorized facility.
5. Amount of public funds expended.
6. Amount authorized for rapid tax amortization.
7. Date of completion of authorized facility.

B. For the period since World War II supply the following information with respect to each facility purchased or leased from the Government by you or by an entity subsequently acquired by you and utilized for antibiotics manufacture, processing or packaging (whether or not originally constructed as an antibiotics facility):

1. Plancor No.
2. Location of facility.
3. Total cost of facility.
4. Total purchase price or lease terms.
5. Amount authorized for rapid tax amortization.

C. For the period 1950–53, inclusive, supply the following information with respect to antibiotics facilities authorized by the Government for construction by you or by an entity subsequently acquired by you:

1. Certificate of Necessity No.
2. Location of facility.
3. Total cost of authorized facility.
4. Amount authorized for rapid tax amortization.
5. Date of completion of authorized facility.

Schedule IX

PURCHASES OF ANTIBIOTICS

Submit a list of all purchases of *all* antibiotic products, whether in bulk or dosage form, which you made 6 months prior to, during, and 6 months after any period during which you were an "original manufacturer" (as the Tariff Commission uses the term, "original manufacturer") of *any* antibiotic substance, giving the following information with respect to each such purchase:

1. The name and address of your supplier. (If your supplier was other than the original manufacturer of the antibiotic purchased, also give the name and address of the original manufacturer.)
2. The generic name of the antibiotic purchased.
3. A product description sufficient to permit a determination of the exact form in which you received delivery of the antibiotic.
4. The unit price you paid.
5. The effective date of this price.
6. The total quantity of the antibiotic purchased.
7. The invoice value applicable to 6.
8. If any of the purchases which you are required by this schedule to report were made under a purchase contract covering a specified time period, submit a copy of each such contract.

NOTE.—You are required to report under this schedule only purchases made with the intent of reselling, either before or after further processing.

SCHEDULE X

EMPLOYEE CLASSIFICATION

For each year 1943 through 1956, provide (a) the number of employees as of the close of the year, and (b) the number of man-years utilized, in each of the following antibiotics activities:

A. Research and development.
B. Manufacturing.
C. Detailmen.
D. Compounding and packaging.
E. All other.

NOTE.—Research-development includes basic and applied research in the sciences (including medicine) and in engineering, and design and development of prototypes and processes. It doe *not* include non-technological activities and technical service, such as quality control, routine product testing, market research, sales promotion, sales service, geological or geophysical exploration, or research in the social sciences of psychology. (This is the definition used by the Bureau of Labor Statistics in the publication for the National Science Foundation entitled, *Science and Engineering in American Industry,* NSF 56–16.)

SCHEDULE XI

SALES IN 1956

A. Indicate for 1956 the approximate percent of total net sales of antibiotic products to each of the following classes of customers:

1. Bulk sales:
   a. Processors and packagers.
   b. Original manufacturers.
   c. Animal feed producers.
   d. Other (specify).
2. Dosage forms:
   a. Federal Government.
   b. State and local governments.
   c. Hospitals and institutions.
   d. Wholesale outlets.
   e. Retail outlets.
   f. Original manufacturers.
   g. Other (specify).

B. Describe, with respect to the detailmen you employ:

1. Method by which they are compensated; e. g., salary, salary plus commission, etc.

2. Policy followed in setting up territories. Include extent of coverage of U. S. and number of men in each territory.

Schedule XII

PRICING POLICY FOR ANTIBIOTICS

1. Name the organizational group, or person, including titles and positions, responsible for determining the price at which you offer each antibiotic product for sale.

2. Describe any consultative or other procedures which the above named group or person customarily employs prior to arriving at the price at which you offer an antibiotic product for sale.

3. Briefly describe the factors customarily given consideration by the responsible person, or group, in setting the price of an antibiotic product.

4. Briefly explain, relative to your pricing procedures for *legend drugs*, any differences which may exist between those applicable to such drugs containing antibiotics and those applicable to such drugs which do not contain any antibiotic.

5. Briefly explain, relative to your pricing procedures for *antibiotic products*, any differences which may exist between those applicable to sterile bulk products and those applicable to dosage forms for human medication.

6. Briefly explain, relative to your pricing procedures *applicable to antibiotic dosage forms for human medication*, any differences which would customarily appear under the following sets of circumstances:

(a) The establishment of the initial price for the first form in which you offered a newly discovered antibiotic, not previously offered by any other company, contrasted with the establishment of the initial price on a product of which at least one virtually identical or closely substitutable product is already being offered by others.

(b) The *increase* of the price of a product for which you and others offer identical or closely substitutable products as contrasted with the *decrease* of the price for such a product.

7. When you reduce a price on a legend antibiotic drug, what has been your policy with respect to retroactive credits to your customers for stocks on their shelves, purchased at higher prices, or, if their customers are resellers, on the shelves of their customers?

8. What has been your practice with respect to the returns, allowances, and credits on antibiotic drugs which carry expiration dates and what consideration is given to this practice in determining price?

9. If, since you began to offer legend antibiotic products for sale, you have changed the pricing policies you formerly followed in pricing legend drugs in any way not covered in your preceding answers to questions in this schedule, please explain briefly.

Notes

1. In this schedule the term "price" is intended to mean any series of prices for various quantities and to all the customer classes to which you offer the product. If your policies with respect to quantity or customer class differentials have varied since you began to offer antibiotic products, please include in your answer to question 9 a description of such changes.

2. If, in response to the report request dated July 20, 1956, you feel that you have answered any of the questions in this schedule, you may simply refer to the appropriate section of that response in order to comply with this schedule.

Schedule XIII

HISTORICAL DATA FOR YEARS 1943 THROUGH 1949

The purpose of this schedule is to provide an opportunity to furnish information which may not fit readily into schedules I through XII, but which may modify or amplify certain of them. It is regarded as possible that some companies may wish to furnish additional information relative to the developmental period of the industry. Such information, for example, might clarify certain of the key relationships, such as those between costs and prices or those involving mergers or acquisitions.

It is recognized that not all companies have maintained detailed records for this period comparable, for example, to schedules I to III. Therefore, no specific outline is suggested for reporting purposes. However, if full information is available it may be reported in the tabular form indicated for schedules I to III.

The Commission may request further detail on these years if, after examination of the information submitted, such information appears necessary.

APPENDIX II

Discovery and Development of Penicillin

Dr. Fleming's early work.—In one of his last papers, Sir Alexander Fleming, the discoverer of penicillin, began by saying:

> The word "Penicillin" first appeared in print 25 years ago in the first article I wrote on "The antibacterial properties of a mould." There I gave the antibiotic spectrum, the remarkable power of diffusion into agar and of inhibiting growth, and facts as to the absence of toxicity so far as could be ascertained in the crude, unpurified fermentation liquor, for that was all we had in those days. It was the first substance I had ever found to be more lethal to organisms like staphylococci or streptococci than it was to leucocytes and this to me was an indication that it approached more nearly the ideal chemotherapeutic agent than any of the antibacterial chemicals that had been described. However, there was no means of knowing how good it really was and in those days I do not think that anybody suspected that a substance would ever be found which would be as good as penicillin has proved to be.[1]

It was only "after various ups and downs," as Fleming put it in 1945, that it became possible to say "now * * * we have penicillin".[2] Much of the history of penicillin is thus a record of vicissitudes that delayed and limited the full recognition of its worth. "The story of penicillin," he said in 1946, referring not only to its discovery but also to the course of its development into a chemotherapeutic agent in worldwide use, "has often been told in the last few years";[3] and it continued to be told in succeeding years, by him and by others, with differences in emphasis and interpretation, and by some with remarkable inaccuracy.

The commonest error in connection with Fleming's first report—an error still extremely prevalent—is that the famous observation was first made in 1929, the year in which the article reporting it was published. The error seems to have been so solidly established that when, years later, Fleming wrote[4] of his encounter with the penicillium as having occurred in September 1928, and did not call attention to the persistent error, the correction was ignored or went unnoticed.

The discovery and development of penicillin has been characterized as "not merely the greatest achievement in chemotherapy, but also one of the greatest achievements in the whole history of medicine".[5] A writer on scientific subjects

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[1] Foreword to "Penicillin: A Symposium," The Practitioner, January 1955, vol. 174, p. 5. What was "aimed at in this symposium, published to coincide with the twenty-fifth anniversary of the publication of Sir Alexander Fleming's first report on his discovery, [was] to provide a critical review of the present status of penicillin. * * *" (Op. cit., p. 1.)

[2] Harvard Alumni Bulletin, vol. 47, p. 580.

[3] Sir Alexander Fleming, "Chemotherapy, Yesterday, Today, and Tomorrow," the Linacre Lecture delivered at Cambridge on May 6, 1946, Cambridge University Press, 1946, p. 30.

[4] No later, however, than the article, "The Discovery of Penicillin," British Medical Bulletin, vol. 2 (1944), No. 1, p. 4.

[5] T. I. Williams, The Chemical Industry, Penguin Books, Melbourne, London, Baltimore, 1953, p. 139.

for the general public has expressed the opinion that "Fleming's first report belongs among the classic scientific observations of all times".[6] An eminent American mycologist several years ago characterized as "now famous"[7] the paragraph with which Fleming began his paper announcing the discovery and naming of penicillin. Because of its intrinsic interest and historic importance the substance of Fleming's account of his discovery will be summarized here, largely in quotations from his 1929 and later writings:

> While working with staphylococous variants a number of culture plates were set aside on the laboratory bench and examined from time to time. In the examinations these plates were necessarily exposed to the air and they became contaminated with various micro-organisms. It was noticed that around a large colony of a contaminating mould the staphylococcus colonies became transparent and were obviously undergoing lysis. * * *
>
> Subcultures of this mould were made and experiments conducted with a view to ascertaining something of the properties of the bacteriolytic substance which had evidently been formed in the mould culture and which had diffused into the surrounding medium. It was found that broth in which the mould had been grown at room temperature for 1 or 2 weeks had acquired marked inhibitory, bactericidal and bacteriolytic properties to many of the more common pathogenic bacteria.
>
> * * * * * * *
>
> A number of other moulds were grown in broth at room temperature and the culture fluids were tested for antibacterial substances at various intervals up to 1 month. * * *

Besides five "other moulds," eight strains of penicillin were grown and examined. Concerning the strains in question Fleming stated:

> Of these it was found that only one strain of penicillium produced any inhibitory substance, and that one had exactly the same cultural characters as the original one from the contaminated plate.
>
> * * * * * * *
>
> In the rest of this article allusion will constantly be made to experiments with filtrates of a broth culture of this mould, so for convenience and to avoid the repetition of the rather cumbersome phrase, "Mould broth filtrate," the name "penicillin" will be used. This will denote the filtrate of a broth culture of the particular penicillium with which we are concerned.

Of this penicillium, Fleming said that "in all its characters it most closely resembles *P. rubrum*." This apparently was based on "suggestions as to the identity of the penicillium" that were offered by the mycologist who, with two colleagues, gave "help in carrying out some of the experiments described."[8]

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[6] Steven M. Spencer, Wonders of Modern Medicine, McGraw-Hill Book Co., Inc., New York, N. Y., 1953, p. 97.

[7] Kenneth B. Raper, "A Decade of Antibiotics in America," Mycologia, vol. 44, No. 1, p. 2.

[8] Cf. Sir Alexander Fleming, "Antiseptics, Old and New" (A Mayo Foundation Lecture given July 16, 1945), Proceedings of the Staff Meetings of the Mayo Clinic, vol. 21, No. 4 (February 20, 1946), p. 71: "* * * We had a little trouble with identification of the mould. Our mycologist who put it through its paces called it 'Penicillium rubrum.' But it made a bright yellow color and even, with my small knowledge of Latin, I thought 'rubrum' did not mean 'yellow.' That name was wrong. Then the mould went to a famous mycologist on the continent of Europe and she called it something else. I have forgotten what, but she was wrong, too. Then the mould was sent to Dr. Thom, here in the United States of America, and he identified it as 'penicillium notatum' although it wasn't quite identical with his stock culture. He was right and lots of strains of penicillium notatum have been found since which make penicillin."

Using suitable techniques for "examining for inhibitory power," the broth filtrate was tested against various microbes, and the results were recorded. From these it was said to be "clear that penicillin contains bacterio-inhibitory substance which is very active toward some microbes while not affecting others." This selectivity was exhibited in the tables presented, but certain bacteria were singled out for comment. Staphylococci, *Streptococcus pyogenes*, and pneumococci were reported to be "very sensitive." Gonococci and meningococci were among those said to be sensitive.[9]

Summarizing the discussion of the toxicity of penicillin it was said: "Penicillin is nontoxic to animals in enormous doses and is nonirritant. It does not interfere with leucocytic function to a greater degree than does ordinary broth." The summary of the paper "suggested that it may be an efficient antiseptic for application to, or injection into, areas infected with penicillin sensitive microbes." Somewhat earlier it had been stated, "Experiments in connection with its value in the treatment of pyogenic infections are in progress." The usefulness of penicillin to the bacteriologist for the isolation in cultures of nonsensitive organisms from bacteria sensitive to penicillin was also noted.[10]

Fleming preserved the culture—in fact he saved the contaminated culture plate to which the activity of the mold had attracted his attention—and he probably deposited it in the National Collection of Type Cultures. At any rate, Dr. Charles Thom believed it to have been there in 1930.[11] Of the original Fleming strain of *Penicillium notatum*, it was reported in 1949: "Fleming has maintained his fungus ever since its original isolation and has freely distributed subcultures to other investigators. In the British National Collection of Type Cultures it now figures as No. 4222, though an earlier isolate appeared in the 1931 catalog as No. 3127." [12] The culture with which Florey and Chain began their work was descended from Fleming's strain, but "had been maintained for some years in the School of Pathology, Oxford." [13] Although it was stated by Fleming in 1945 that when "Florey, Chain, and their co-workers at Oxford took up the work [on penicillin] they got our cultures," [14] he was probably thinking of a time somewhat later than the beginning of the Oxford investigations. At any rate, in a Lancet article of 1941 it was said: "The strains of penicillium used in this work have been obtained from Prof. Alexander Fleming of St. Mary's Hospital, London." [15]

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[9] Writing years later of the specific action of penicillin as first observed, Fleming noted as "interesting that the bacteria originally found to be sensitive in this way to the crude culture fluid are the same as those which have subsequently been found to be affected by concentrated penicillin used clinically." (Alexander Fleming, "The Discovery of Penicillin," British Medical Bulletin, vol. 2 (1944), No. 1, p. 5.)

[10] Fleming, Alexander, "On the Antibacterial Action of Cultures of a Penicillium, With Special Reference to Their Use in the Isolation of *B. Influenzae*," The British Journal of Experimental Pathology, vol. X, No. 4 (August 1929), pp. 226–236.

[11] Charles Thom, "Mycology Presents Penicillin," Mycologia, vol. 37 (1945), p. 461.

[12] Florey, H. W.; Chain, E.; Heatley, N. G.; Jennings, M. A.; Sanders, A. G.; Abraham, E. P.; Florey, M. E., Antibiotics, 2 vols., Oxford University Press, London, New York, Toronto, 1949, p. 673. (This work will hereinafter be cited: H. W. Florey, et al., Antibiotics, p. —.)

[13] H. W. Florey et al., Antibiotics, p. 673, Cf. also Leslie A. Falk, "The History of Penicillin, Journal of the American Medical Association, vol. 124, No. 17 (April 22, 1944), p. 1219.

[14] Antiseptics, Old and New (A Mayo Foundation Lecture given July 16, 1945), proceedings of the staff meetings of the Mayo Clinic, vol. 21, No. 4 (February 20, 1946), p. 72.

[15] Abraham, E. P.; Chain, E.; Fletcher, C. M.; Florey, H. W.; Gardner, A. D.; Heatley, N. G.; and Jennings, M. A., "Futher Observations on Penicillin," Lancet 2, August 16, 1941, p. 178, n. 2.

In a paper published in 1944, Fleming wrote:

> I have used penicillin constantly since 1929 for differential culture, but its use for practical therapeutic purposes remained in abeyance until the Oxford workers started their investigations.[16]

Contributions of Raistrick and His Associates

In 1930, at the London School of Hygiene and Tropical Medicine, Prof. Harold Raistrick and co-workers undertook certain chemical studies of the products of Fleming's mould which, in circumstances to be recounted later, had been identified by Dr. Charles Thom of the United States Department of Agriculture. Penicillin was produced in a synthetic medium and work was done on the isolation of the antibacterial substance. In the judgment of Florey, expressed in 1949, "important observations were made on the active substance in the metabolism fluid and on its behavior toward solvents. However, penicillin was not extracted and no further investigation was made of its chemical or biological properties since at that time it was believed to be too labile to make further study worthwhile." [17] Nevertheless, without its having been realized, "the first steps toward a successful extraction had in fact been taken." [18]

When, therefore, in 1938, Chain and Florey were considering whether or not to undertake the study of penicillin, the report of Raistrick and his co-workers helped them to a decision. Chain and Florey described the influence of Raistrick and his co-workers as follows:

> * * * both Fleming (1932) and Clutterbuck, Lovell & Raistrick (1932), had stated that pencillin activity might, under certain conditions, be retained in the culture medium for some weeks. It seemed worthwhile to see whether appropriate conditions could be found for extracting the substance, so that further examination of both its biochemical and biological properties could be made.[19]

"Although," it has been said, "there was nothing sensational about" the discoveries at the London School of Hygiene, "it must be remembered that the properties described by Raistrick and his colleagues are fundamental to the methods adopted later for the concentration and purification of penicillin and, indeed, still remain the basis of manufacturing processes." [20]

During the years that penicillin was being neglected as a practical medical discovery it was, in that aspect, as much neglected by its discoverer as by anyone else who was aware of it. In general terms, Fleming attributed the failure of the early investigators to develop pencillin as a therapeutic agent to inadequate assistance. In his 1946 Linacre Lecture, Fleming told how penicillin was discovered and what was shown as to its antibacterial properties by the experiments he was able to make. But, he explained, "I failed to concentrate this substance from lack of sufficient chemical assistance. * * *" Further, reverting to this subject in the same lecture, he said:

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[16] Alexander Fleming, "The Discovery of Pencillin," British Medical Bulletin, vol. 2 (1944), No. 1, p. 5.

[17] H. W. Florey et al., Antibiotics, p. 65.

[18] Ibid., p. 634.

[19] E. Chain and H. W. Florey, "The Discovery of the Chemotherapeutic Properties of Penicillin," British Medical Bulletin, vol. 2 (1944), No. 1, p. 5.

[20] A. L. Bacharach and B. A. Hems, "Chemistry and Manufacture of Penicillin," Penicillin, Its Practical Application, Sir Alexander Fleming, general editor, 2d ed., Butterworth & Co., Ltd., London, 1950, p. 26. (This book will hereinafter be cited: Penicillin, Its Practical Application, 2d ed., London.)

> * * * Discovered here in 1928 in a hospital bacteriological laboratory where the chemical facilities were lacking, then worked on in a biochemical laboratory where the bacteriological cooperation failed, [penicillin] had to wait 10 years before it was concentrated sufficiently to show its remarkable chemotherapeutic properties. Even then there were difficulties in developing it in this country, with the result that the Americans have reaped a large part of the reward.[21]

Again, having noted that his "earliest attempts at concentration failed," Fleming summarized the findings of Raistrick and his colleagues: "They demonstrated," he said, that penicillin "could be extracted from the culture fluid * * *, but in their process a large part of the penicillin was destroyed. Difficulties arose, however, over bacteriological cooperation, which was absolutely necessary, as there was and still is, no satisfactory method other than a bacteriological one for testing the potency of the extracts. In 1932 they published their results and transferred their attention to other problems.[22] I had failed to advance further for the want of adequate chemical help. Raistrick and his associates had lacked bacteriological cooperation, so the problem of the effective concentration of penicillin remained unsolved." [23]

But it is not only in connection with their efforts toward the concentration and purification of penicillin that Raistrick and his co-workers have a place in the history of penicillin. Another contribution toward the eventual quantity production of penicillin, although unwitting and of unforseeable significance when made, was Raistrick's sending to Dr. Thom for identification a culture of Fleming's mold. How this occurred was reported by Thom in 1945 as part of an account of the coming of "the Fleming organism" to America and its first 10 years here:

> On April 29, 1930, Prof. Harold Raistrick of the School of Tropical Medicine in London wrote as follows to Thom in Washington: "The other culture, labeled *P. rubrum* (?), was received from the British collection of type cultures and bears their catalog number 3127. It was originally isolated by Dr. Alexander Fleming of St. Mary's Hospital, London, and is described by Fleming in a paper [24] * * *. I am carrying out a piece of work on this species and since, as you will see if you refer to the original paper, this diagnosis of it is very doubtful, I wonder if you would be good enough in this case to let me have an authoritative statement as to its identity." A culture of the Fleming organism accompanied the letter. * * * Raistrick's laboratory began work with it before May 1, 1930, hence it was available to any worker. Raistrick, from his own knowledge of molds, did not accept the identification of this organism as *P. rubrum*. * * * To that letter, I replied (June 30, 1930): "For this other culture, however, I am obliged to you since I was anxious to know what Fleming's organism would be like. I have cultivated it under several different conditions and cannot agree with his nomenclature as *P. rubrum*. * * * In fact, I believe his culture although showing some divergences in culture reaction, to be closer to

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[21] Sir Alexander Fleming, "Chemotherapy Yesterday, Today, and Tomorrow," the Linacre Lecture delivered at Cambridge, Cambridge University Press, 1946, pp. 30, 37.

[22] "According to Ludovici, 'the mycologist who had been assisting' Raistrick and his associates 'was killed in an accident and in the autumn of 1932, the bacteriologist in the team resigned his appointment to go elsewhere.' " (L. J. Ludovici, Fleming, Discoverer of Penicillin, Andrew Dakers, Ltd., London, 1952, pp. 146–147.)

[23] Alexander Fleming, "History and Development of Penicillin," Penicillin, Its Practical Application, 2d ed., London, pp. 11–12.

[24] This was his first paper on penicillin, published in the British Journal of Experimental Pathology, vol. X, No. 4 (August 1929).

P. notatum of p. 264 in my book than to the group discussed on pp. 249 to 250 as indicated by the nomenclature used" (by Fleming). The culture received from Raistrick was put in the Thom collection as 144.5112.1. The corrected name appears in Raistrick's papers and was accepted by Fleming in his 1932 paper.[25] Nevertheless, requests for *P. rubrum* were frequently received during the several succeeding years. These were usually answered by sending the Fleming culture and a letter explaining the corrected nomenclature." [26]

Although Raistrick's research led to the correct identification of the penicillium mold, it did not produce penicillin in concentrated form, and progress in solving this problem thereafter lagged for several years.

Investigation of Penicillin at Oxford

H. W. Florey, who took a leading part in the discovery of the therapeutic properties of penicillin at Oxford in 1940, states that in 1929 he became interested in another discovery of Fleming known as lysozyme.[27]

How study of the antagonism of lysozyme to certain bacteria eventually led to further research on penicillin has been described by the Oxford collaborators as follows:

> In the course of numerous discussions on lysozyme, and on the phenomenon of microbial antagonism, Chain and Florey decided to undertake jointly a systematic investigation of some of the antibacterial substances produced by micro-organisms. In view of this program they submitted an application for financial help to the Natural Sciences Division of the Rockefeller Foundation in November 1939, * * *.[28]

In making their application for a grant, Florey and Chain stated:

> In view of the possibly great practical significance of antagonistic substances produced by bacteria against bacteria it is proposed to study systematically the chemical fundamentals of the phenomenon with the aim of obtaining in purified state and suitable for intravenous injection bacteriolytic and bactericidal substances against various kinds of pathogenic micro-organisms. A beginning has already been made here with the purification of the bactericidal substances produced by *Penicillium notatum* and *B. pyocyaneus*. The experience obtained in the Department during the prolonged studies on the mechanism of the action of lysozyme, is of course, of great value in the study of these problems which are so closely related to and, in fact, emerged from the lysozyme studies.[29]

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[25] Cf. Sir Alexander Fleming, "History and Development of Penicillin," Penicillin, Its Practical Application, 2d ed., London, p. 14: "In 1930 Raistrick had sent a culture of the strain, which he had received from me, to Thom to confirm his suspicion that the name first applied to it (*P. rubum*) was wrong."

[26] Charles Thom, "Mycology Presents Penicillin," Mycologia, vol. 37 (1945), pp. 461–462.

[27] Cf. H. W. Florey, "Penicillin: Its Development for Medical Uses," Nature, January 8, 1944, vol. 153, p. 40, where Florey described lysozyme as "a substance occurring in many animal tissues and secretions which has the power of dissolving certain air bacteria, though unfortunately none which produces disease." Dorland's Illustrated Medical Dictionary, 23d ed. (1957), gives the following medical definition: "Lysozyme, a crystalline, basic protein, which is present in saliva, tears, egg white and many animal fluids and which functions as an antibacterial enzyme, especially effective in lysing *Micrococcus lysodeikticus*."

[28] H. W. Florey, et al., Antibiotics, p. 636.

[29] H. W. Florey, et al., Antibiotics, p. 637.

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Work initiated with the financial support of the Rockefeller Foundation led to the discovery at Oxford of the therapeutic properties of penicillin in 1940. Following the success of these studies, statements concerning the motivation of the work frequently appeared. Since these were often erroneous the collaborators have on various occasions undertaken to set the record straight, as in the passage below:

> Although in the application the possible practical results were brought forward, the research was conceived of as an academic study with possibilities of wide theoretical interest, both chemical and biological. Statements have appeared from time to time that the work on penicillin was started as an attempt to contribute to the treatment of septic wounds in World War II. This is quite erroneous, as the work was planned well before the outbreak of war, and in any case there was then no idea that penicillin could play the important part which it has done in the treatment of war injuries.[30]

As Florey and his collaborators report in their two-volume work, Antibiotics, "it was not until late in 1939 that work on penicillin was taken up vigorously by Chain, Florey, and Heatley." [31] One of the important achievements of this early stage was a new assay method devised by Heatley. "After an antibiotic effect has been detected * * * little or no progress can be made in the further investigation of the agent or agents responsible for the effect without suitable assay methods. These are necessary not only for each step in the isolation of the antibiotic, but in almost every kind of investigation on it, for instance for pharmacological and certain chemical studies, methods of purification and production." [32]

"At first the mould was grown in flasks" [33] while "the initial experiments were concerned with finding reproducible conditions for obtaining penicillin in what was then considered a satisfactory yield, and in a preliminary study of its chemical properties. This work, carried out by Chain and Heatley, confirmed and extended the observations of Clutterbuck, Lovell, and Raistrick" [34] reported in 1932. An important advance in knowledge was made when the experiments of the earlier workers were repeated and their observations confirmed, and it was demonstrated that penicillin could be extracted from the crude brew and partially purified.[35]

> Attempts to obtain penicillin salts in a dry state showed that aqueous penicillin solutions could be evaporated to dryness *in vacuo* from the frozen state without loss of activity, and eventually a small amount of hygroscopic brown powder, containing the sodium salt of penicillin, was obtained. * * * It is interesting to note that solvent transfer and lyophilization still [1949] form the basis of all commercial penicillin production processes. The brown

[30] Ibid., p. 637.

[31] Ibid.

[32] H. W. Florey et al., Antibiotics, p. 110, ch. 3 of this work, pp. 110–199, was written by N. G. Heatley. Cf. Dr. John F. Fulton, "Penicillin, Plasma Fractionation, and the Physician," the Atlantic Monthly, September 1945, p. 109: "Dr. Norman Heatley of Florey's team must be given principal credit for developing methods of assay. The strength of each new strain had to be tested; without testing methods it would have been impossible to determine the effectiveness of the different molds or of the various methods of extraction." Cf. also, the editorial, "The History of Penicillin," Journal of the American Medical Association, vol. 126, No. 3 (September 16, 1944), p. 170.

[33] H. W. Florey, "Penicillin: Its Development for Medical Uses," Nature, January 8, 1944, vol. 153, No. 3871, p. 41.

[34] H. W. Florey et al., Antibiotics, pp. 637–638.

[35] H. W. Florey, "Penicillin: Its Development for Medical Uses," Nature, January 8, 1944, vol. 153, No. 3871, p. 41, which see for details.

powder containing the sodium salt of penicillin retained its activity for some time when kept dry. Its antibacterial power was high when compared with that of other antibacterial agents such as the acridine derivatives and the sulphonamides, as it inhibited the growth of staphylococci at a dilution of 1 in 500,000. At that time the enormous power of pure penicillin was not realized and it was thought possible, in view of the great antibacterial strength of the brown powder, that the sodium salt of penicillin had been obtained in a fairly high degree of purity. In actual fact subsequent investigations showed that the preparation had contained less than 1 percent of penicillin.[36]

As soon as it became possible, bacteriological work was carried on concurrently with the study of the physical and chemical properties of penicillin. "While this chemical and bacteriological work was proceeding, investigations were also made on its pharmacological properties," in connection with which Florey listed the following as "the most important points":

(1) Lack of toxicity to mice and other animals.

(2) White blood cells (leucocytes) and tissue cultures (body cells grown in glass vessels) are unaffected by concentrations of penicillin some hundreds of times greater than that necessary to stop bacterial growth.

(3) The activity of penicillin is not affected by pus, blood or the breakdown products of dead tissues.

(4) Its activity is little affected by the number of bacteria present.

(5) It is absorbed after injection into muscle or beneath the skin and from the small intestine.

(6) It cannot be given by stomach owing to the presence of acid there, nor by the large bowel owing to the presence of bacteria which destroy it.

(7) It is very rapidly excreted by the urine, hence large and frequent doses have to be given. It is also excreted in the bile.

Points 3 and 4 are in sharp contrast to the sulphonamides.

It is most important that penicillin has little effect on the white blood cells or leucocytes, for it is to these that we owe a great deal of the capacity of the body to combat infection. * * *

* * * in combating bacteria which have gained entry to the body, [penicillin] * * * stops the growth of the germs, while the white blood cells ingest them and kill them off.[37]

Laboratory experiments known as mouse protection tests[38] were conducted, regarding the first of which it has been stated:

imperfect as it was, [it] sufficed to give grounds for the hope that penicillin would have some systemic chemotherapeutic properties so that it was clear that further investigation should be carried out with as great a speed as possible. * * * [Therefore] the collaboration of other workers [was obtained; and as new problems arose or old ones ramified, appropriate special-

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[36] H. W. Florey, et al., Antibiotics, p. 638.

[37] H. W. Florey, "Penicillin: Its Development for Medical Uses," Nature, January 8, 1944, vol. 153, No. 3871, p. 41. "The final experiments which demonstrated that penicillin might be useful in medicine were those known as mouse protection experiments. A number of mice are inoculated with germs which will certainly kill them if no successful treatment is given. We sat up through the night injecting penicillin every 3 hours into the treated group, and I must confess that it was one of the more exciting moments when we found in the morning that all the untreated mice were dead and all the penicillin-treated ones alive. The diseases treated experimentally, were caused by the streptococcus, the staphylococcus and a gas gangrene organism. Against the latter two organisms there is no other really effective drug."

[38] Cf. H. W. Florey, "Penicillin: Its Development for Medical Uses," Nature, January 8, 1944, vol. 153, No. 3871, pp. 41–42.

ists were, as needed, enlisted to deal with them.] Thus the group of workers, now sometimes referred to as the Oxford team, was gradually assembled and their work was greatly facilitated by the devoted labours of the * * * technical assistants. * * * The work was much accelerated by the most intimate collaboration of all concerned and the success attained was undoubtedly due to the combined efforts of the members of the group.[39]

Further mouse protection tests were carried out between the last week of May and early July 1940. Although their scope was limited because the supply of penicillin was very small, their results were highly important. Regarding them, Florey subsequently said:

> The gratifying results of the first mouse protection experiments led to the immediate realization of the possible therapeutic value of penicillin in man, especially in the war-wounded, and it was at once decided to explore every possible means of obtaining enough of the material for preliminary trials of the drug in infections in man. The enthusiasm of the Oxford workers was believed by many to be premature, and though an approach was made to a commercial firm, this firm and others who might otherwise have helped in the project were overburdened with war work. It was shortly afterwards, too that the worst period of enemy bombing began in England (September 1940).[40]

These adverse circumstances added greatly to the difficulty faced by the Oxford group in obtaining larger quantities of penicillin needed for further clinical research. According to Florey—

> * * * because of this and other difficulties in industrial production it was determined to undertake in the laboratory at Oxford the brewing and extraction of sufficient material for trials on disease in man. For it was clearly realized that unless results could be obtained in man as striking as those in the animal experiments it was highly improbable that any firm would embark on production on a sufficiently large scale.[41]

In commenting on the much larger quantities of penicillin needed for clinical testing on man than had previously been used on mice, Florey has written:

> A man is roughly 3,000 times the weight of a mouse, so you can well imagine that the next step, to produce enough to use on man, took months of labor on the scale at which we were then working. Eventually enough was made to give a single small injection to a man. Much to our consternation, the patient started shivering and the temperature rose. Fortunately, the substance causing this reaction was not penicillin, and the impurity was removed quite easily by chemical means.[42]

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[39] H. W. Florey et al., Antibiotics, pp. 638–639. Cf. Gladys L. Hobby: "The reports by Florey and his co-workers on the nature and action of penicillin are classic in that they represent the first instance in which a complete evaluation of a drug was carried out by a single group of investigators. Attention was called to a fact, now well accepted, that only by a combination of bacteriological, biochemical, and biological methods can a reasonably accurate picture of an antimicrobial or chemotherapeutic agent be obtained. For the first time the potentialities of antimicrobial agents of natural origin in the treatment of systematic [sic] infections were established conclusively." (Journal of the History of Medicine and Allied Sciences, vol. VI, No. 3 (summer 1951), pp. 372–373.

[40] H. W. Florey and E. P. Abraham, "The Work on Penicillin at Oxford," Journal of the History of Medicine and Allied Sciences, vol. VI, No. 3 (summer 1951), p. 306.

[41] H. W. Florey et al., Antibiotics, p. 642.

[42] H. W. Florey, "Penicillin: Its Development for Medical Uses," Nature, January 8, 1944, vol. 153, No. 3871, p. 42.

In discussing these difficulties in other writings, Florey later said:

> The difficulties in raising the scale of laboratory production were formidable, and the decision had to be taken whether it would be more profitable to struggle on with the methods already in use, which gave only a tiny yield per litre of culture fluid, until enough had been made for trial in man, or whether to hold up production while a search was made into possible means of increasing the yield. The former policy was adopted, rightly as it seems now, for once the chemotherapeutic effectiveness of penicillin in man had been demonstrated the impulse to further work became sufficient to make the provision of facilities for the subsequent large-scale investigations by industrial and other research bodies a matter of high priority. However, at the same time as laboratory large-scale brewing was being carried out, attempts were made at Oxford to increase the yield by changing the composition of the medium and by selecting high-yielding strains. Among those tested were single spore isolates from the strain already in use and from cultures obtained towards the end of 1940 from Fleming. These investigations gave no useful results at the time, though more extended work on similar lines which was done later in America was highly successful.[43]

By means of experiments with animals, the "mouse protection tests" in particular, "a fairly complete knowledge of its properties, both chemical and biological, had been obtained before penicillin was used on man."[44] Discussing the earliest cases several years after they had been treated, Florey and his associates wrote:

> It was natural that the first infections made available for treatment were nearly all of the most severe type and those in which every other available treatment had failed, and it is perhaps well that desperate cases should have been used at first, for the results became thereby more significant and easier to interpret. Five of the first six patients had staphylococcal or streptococcal infections which could not be controlled by surgical and sulphonamide therapy. The first, the treatment of whom was begun at the Radcliffe Infirmary on February 12, 1941, had a severe staphylococcal infection with abscess formation and osteomyelitis. At that time little was known about how long the treatment might have to be continued, and after 5 days, when considerable clinical improvement had taken place, the meager stock of penicillin was exhausted and the patient eventually relapsed and died.[45]

For the treatment of the second patient, also, the supply of penicillin proved to be insufficient. The third, fifth, and sixth cases made recoveries, one member of this group being "the first patient to receive continuous intravenous penicillin." In the fourth case, penicillin was administered for 9 days "and led to a steady improvement. The boy was apparently restored almost to normal when he died

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[43] H. W. Florey, Antibiotics, p. 642. How formidable these difficulties were has been stated more explicitly as follows: "At that time the best titer obtained in the metabolism liquor was about 2 units per ml., and the best final recovery after extraction was seldom as high as 40 percent. Thus the preparation of 1 million units for clinical use required at least 1,500 liters (400 U. S. gallons) of crude culture fluid, entailing the cultivation of 1,000 square feet of mycelium. For an ordinary research institute, cultivation on this scale, as well as the labor of extracting and concentrating the active substance, was formidable * * *." (H. W. Florey and E. P. Abraham, "The Work on Penicillin at Oxford," Journal of the History of Medicine and Allied Sciences, vol. VI, No. 3 (Antibiotics number, summer 1951), p. 307.)

[44] E. Chain and H. W. Florey, "The Discovery of the Chemotherapeutic Properties of Penicillin," British Medical Bulletin, vol. 2 (1944), No. 1, p. 6.

[45] H. W. Florey et al., Antibiotics, p. 648.

on the 18th day" of a cause other than the infection for which he had been treated with penicillin. Florey and his coworkers further thought that "it is of interest that several of the patients were children. They were chosen in the hope that less penicillin would be needed to treat them than to treat adults. As a further indication of the scarcity of the drug it may be noted that in these early cases the urine was collected and the drug reextracted and used again." [46]

Some of the difficulties met at Oxford when efforts were being made to build up a supply for use in clinical testing are indicated in accounts given by Florey and his associates of the problem of obtaining fermentation vessels. These accounts are combined below:

> The experiments on mice had been done with material grown in Erlenmeyer flasks and extracted by hand in separating funnels. But conical flasks were wasteful of autoclave and incubator space and in any case were not available in sufficient number.[47]
>
> * * * Apart from the usual laboratory ware, trials were made with various kinds of glass and enamel domestic dishes and utensils, and biscuit and other tins (both with and without a coating of lacquer or varnish), but it was found that the old-style bedpan with a side-arm and lid was an ideal culture vessel, providing a relatively large surface area over a shallow layer of fluid and with a side-arm for inoculation and withdrawal. Unfortunately when an effort was made to procure 600 of these vessels, it was found that such a large number could not be provided as they had been replaced by a more modern streamlined structure without a lid. At the time they were required the Battle of Britain had been won but the country was being subjected to heavy bombing so that it was difficult to secure supplies of any sort. Glass vessels could not be made within a reasonable time, but Messrs. J. Macintyre & Co., of the Staffordshire pottery industry, undertook to make special rectangular porcelain vessels, fitted with a side-arm, which could be readily stacked in incubator and sterilizer. * * * To overcome transport difficulties Heatley borrowed a van and drove 200 miles to fetch the first consignment. He returned with them in a snowstorm on 23 December and they were first sown with *Penicillium notatum* on Christmas Day, 1940.[48]
>
> * * * They were inoculated with a spore suspension and incubated at 24° C. in the laboratory operating theatre (already fitted with thermostatically controlled heating), being stacked on discarded bookcases from the Old Bodleian Library. The maximum titer was reached after 6 to 7 days, when the medium was harvested. * * * [49]

The earliest financial encouragement of the work on penicillin at Oxford received from an outside source came from the Rockefeller Foundation. The foundation continued its support during the crucial stages of the research program, recognized the significance of the results not yet completely demonstrated, provided the grant which made possible the visit of Drs. Florey and Heatley to the United States in the summer of 1941, and thereafter supported subsequent antibiotic research.[50] The part played by the foundation in connection with penicillin,

[46] H. W. Florey et al., Antibiotics, pp. 647–649.

[47] Florey, H. W., and Chain, E., "The Work on Penicillin at Oxford," Journal of the History of Medicine and Allied Sciences, vol. VI, No. 3 (summer 1951), p. 307.

[48] H. W. Florey et al., Antibiotics, p. 643.

[49] Florey, H. W., and Chain, E., "The Work on Penicillin at Oxford," Journal of the History of Medicine and Allied Sciences, vol. VI, No. 3 (summer 1951), p. 307.

[50] Since Florey and his associates took some pains to supply financial details, it seems advisable to quote what they reported: "As misleading statements have been made from time to time about the expenditure of money on the early work with penicillin at Oxford,

from its first interest in this potential therapeutic agent down to the end of 1943, is related as follows in the Rockefeller Foundation annual report for 1943:

> In May 1936 The Rockefeller Foundation received a letter from Dr. H. W. Florey, professor of pathology at Oxford, applying for a grant in aid of $1,280. Dr. Florey, who was a former Rockefeller Foundation fellow, explained that he was developing a chemical approach to problems of pathology. He had recently added a biochemist to his staff and had engaged a second chemist to join the group in September; the funds were needed to provide laboratory equipment.
>
> The grant was made at once, and seldom has so small a contribution led to such momentous results. For it was this laboratory, this equipment and this group under Dr. Florey that pioneered the clinical use of penicillin.
>
> The existence of penicillin as a curious byproduct of the greenish-blue mold, *Penicillium notatum*, had been discovered several years before by Dr. Alexander Fleming working at St. Mary's Hospital in London. Dr. Fleming first recognized its antagonism to bacteria * * * when he found that certain bacteria disappeared in the presence of the mold. In a sense the discovery was an accident, but as Pasteur remarked, "Chance favors the prepared mind." Dr. Fleming followed his discovery with various tests of the ability of *Penicillium notatum* to clear up colonies of microbes in a test tube. But no tests had been made of its medicinal value, and Dr. Florey and his associates at Oxford now undertook, as one of their projects, to explore its possibilities in the treatment of human disease.
>
> Toward the end of 1939, with England engaged in a war of survival, Dr. Florey sent the foundation a brief prospectus of his proposed research, the groundwork for which had been laid in the intervening years. He headed it "A Chemical Study of the Phenomenon of Bacterial Antagonism," and he asked for $5,000 for a year's support—a sum which was immediately put at his disposal. By the end of 1940 he was able to write the foundation "There is good ground for hoping that this substance will be much more effective than the sulfonamides, hence the prosecution of the work is of urgency and importance." And the conservative scientist added: "I don't think I am too optimistic in thinking that this is a very promising line."
>
> A second grant of $5,000 was made, and in April 1941 Mr. Warren Weaver, head of the foundation's division of natural sciences, visited Dr. Florey in England. In his diary of the visit, Mr. Weaver recorded this observation: "This project, if it were indeed successful, would be more revolutionary than the discovery of the sulfa drugs, and must be recog-

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and questions asked in Parliament, it may be in the interest of historical accuracy to state the following facts. In the first place the laboratory where the work was done, and some of the salaries and the materials, were supplied by Oxford University—a fact sometimes forgotten. As is the usual practice for financing research at the present time, the contributions made by the University were supplemented by grants from other bodies. Thus, for the research on penicillin and, from 1942 onwards, for a gradually increasing amount of collateral work on other antibiotics, the Medical Research Council contributed £8,287 in the years 1939 to 1945, the Rockefeller Foundation £6,140 between 1940 and 1945, and the Nuffield Provincial Hospitals Trust £5,646 between 1943 and 1945.

It is difficult to say exactly when the research on penicillin itself reached a maximum, for in the later years much energy was devoted to the investigation of other antibiotics, and these figures represent the total sums of money spent on both purposes. At no time was the work held up by lack of funds, although it was felt by some that the tenure of appointment and stipends of the academic research workers in this type of work left something to be desired. (H. W. Florey et al., Antibiotics, pp. 669–670.)

nized as a project of the very highest potential importance. We certainly ought to do all that we can to accelerate its progress."

In July 1941 the foundation provided a special travel grant to enable Dr. Florey and his associate, Dr. N. C. Heatley, to visit the United States. The purpose of the visit was to make the experience of the Oxford Laboratory accessible to American workers. * * * [51]

Transfer of Research and Production to the United States

In reporting the first steps taken when they reached the United States, Florey and his collaborators have stated:

* * * They arrived just before the celebrations of July 4, and spent the first few days with Dr. J. F. Fulton at New Haven. After the situation had been explained to him he suggested that they see Dr. Ross Harrison, president of the National Academy, who advised them to talk to Dr. Thom of the Bureau of Plant Industry at Beltsville, Md. Dr. Thom took them to see Dr. Wells at the Department of Agriculture in Washington, and after a very friendly discussion it was agreed that they should go to the Northern Regional Research Laboratory of the Department of Agriculture at Peoria.[51a]

Dr. Thom also thought it worth recording how connections were established for Florey and Heatley with the Northern Regional Research Laboratory. He stated:

There are discrepancies in the stories told as to what happened in New York * * *. Enough that Florey and Heatley did not establish American connections from the Rockefeller offices in New York. The Rockefeller Foundation sent them to the Medical Section of the National Research Council in Washington on July 8, 1941. Since problems concerning *Penicillium* had long been handled in the Department of Agriculture, the project was referred to us directly by telephone. Arrangements were completed by telegraph on July 9th to turn the project over to the Northern Regional Research Laboratory of the U. S. Department of Agriculture at Peoria, Ill., and on July 13th Florey and Heatley were in the Peoria laboratory where they had the cooperation of a group of men with long experience in mold fermentation, including Herrick, May, Coghill, Ward, Raper, Moyer, and others. Florey stayed only a few days, then turned to other interests; Heatley continued in Peoria for a time, * * *.[52]

In describing further what happened during their visit, the British scientists have stated:

The problem of producing more penicillin was put to the Director of the Laboratory, Dr. May, and to the Director of the Fermentation Division, Dr. Coghill. It is worth noting, in view of subsequent developments, that at that first meeting on July 14, 1941, Coghill asked whether deep fermentation on the lines of that used for the production of gluconic acid had been tried and suggested that this might be the key to successful commercial production. Florey then visited a number of drug firms in the United States and Canada with a request which now looks modest but

[51] "President's Review," The Rockefeller Foundation Annual Report for 1943, New York, 1944, pp. 6-8.

[51a] H. W. Florey et al., Antibiotics, p. 249.

[52] Charles Thom, "Mycology Presents Penicillin," Mycologia, vol. 37, 1945, pp. 466–467.

at the time seemed formidable—to brew 10,000 liters of culture fluid and extract the penicillin, so that more clinical trials might be made at Oxford. None of the information which had been accumulated at Oxford was withheld. Though certain of the firms thought the matter worth attention, a number of them showed little interest, and some none at all.[53] Amongst the first to tackle the problem seriously were Merck & Co., Inc., E. R. Squibb & Sons, and Charles Pfizer & Co., Inc.[54]

In August, Florey visited the Mayo Clinic. An account of this visit was given by Dr. Wallace E. Herrell:

> Dubos, of the Rockefeller Institute, had informed Florey shortly after his arrival in America of our interest at the Mayo Clinic in studies on antibiotic agents,[55] including our preliminary studies on penicillin. I was glad to receive word from Dubos saying that Florey was coming to visit our laboratories after his stay at Peoria. Dorothy Heilman and I had been working with penicillin since the early part of 1941. Florey expressed satisfaction with the studies we had underway. He also had Heatley supply us with approximately 100 mg. of penicillin. Half of this material had been prepared in the laboratories at Oxford and was called at that time Batch NH2 and contained 42 units of penicillin per milligram; the other half was from that small supply which had been recovered from the urine of one of the patients treated at Oxford and was called Batch NHU6 and contained 20 units per milligram. Heilman and I profoundly appreciate the interest and helpful suggestions given us by Florey in connection with our work on penicillin. I often think of his entirely respectful but humorous reference to the brilliant group at Peoria as the "mold merchants."
>
> I had the pleasure of introducing Professor Florey to the members of the staff of the Mayo Clinic at its weekly meeting on August 20, 1941. My colleagues and I were much impressed with his report, which was based on the material contained in his article which appeared in "Lancet" for August 16, 1941. Florey described, in addition to the experimental studies, the clinical results obtained in ten cases at Oxford. These cases represented the first attempts to use penicillin systemically for treatment of man.[56]

Mentioning the "experimental studies on the antibacterial activity of penicillin * * * begun at the Mayo Clinic in the early part of 1941," Herrell reported: "Through the kindness of Dawson,[57] we had received a transfer of Fleming's culture. * * *"[58]

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[53] In a "report to Dr. Weaver on the visits he had made during the summer," Florey listed "the commercial firms he visited, without dates, as being: the Eli Lilly Co.; Connaught Laboratories, Toronto; Johnson & Johnson; Merck & Co.; Sharp & Dohme; Eastman Kodak; Squibb; and the Lederle Laboratories." (Frank Blair Hanson, Associate Director, The Natural Sciences, The Rockefeller Foundation, to A. N. Richards, May 10, 1943, NA, RG 227.)

[54] H. W. Florey et al., Antibiotics, pp. 649–650.

[55] Pioneer studies of tyrothricin and its components had been made at the Mayo Clinic, and some of them had been reported, prior to Florey's visit. See Wallace E. Herrell, Penicillin and Other Antibiotic Agents, W. B. Saunders Company, Philadelphia, Pa., 1945, Chapter XXI, "Tyrothricin (Gramicidin and Tyrocidine)." The references appended to that chapter include both the early papers on tyrothricin by Dorothy H. Heilman and W. E. Herrell, and later ones by the same authors.

[56] Wallace E. Herrell, Penicillin and Other Antibiotic Agents, W. B. Saunders Co., Philadelphia, Pa., 1945, p. 7.

[57] Dr. M. H. Dawson, of Columbia University. He and his associates were the first American investigators of penicillin as a chemotherapeutic agent.

[58] Wallace E. Herrell, op. cit., p. 9.

The total quantity of penicillin that Florey and Heatley brought with them must have been small. As for their "penicillin-producing culture," Dr. Thom stated:

> [this] strain * * * (also a Fleming derivative) was brought to America by Drs. Florey and Heatley and delivered to me personally on July 9, 1941. To ensure a separate record it entered the collections as 144.5767. It was passed by Heatley to the Northern Regional Laboratory at Peoria and to an unlisted number of manufacturing laboratories, hence derivatives from Heatley's strain may appear anywhere.[59]

Writing some years later of Florey and Heatley's trip to America in the interest of penicillin production, Fleming wrote, "This was not the first time that the penicillin-producing strain of *P. notatum* had reached the mycologists in America." Fleming then proceeded to relate how "Raistrick had sent a culture of the strain, which he had received from [Fleming] to Thom" for identification in 1930.[60]

Thom's correct identification was made in 1930. Speaking years later of its importance to the work begun in Peoria as a result of the visit of Florey and Heatley in the summer of 1941, Thom stated that—

> * * * recognition of Fleming's organism as one of the great and universally distributed *Penicillium chrysogenum-notatum* group opened at once, as we saw it, the possibility that research among related organisms would show penicillin production to be common to the group, hence would enable us to choose among available penicillin-producing forms. * * *
>
> In the case of penicillin, the English workers long insisted that penicillin is produced only by Fleming's organism and its derivative strains. Finally, however, Raper, Alexander, and Coghill, working in Peoria, piled up proofs that strains isolated from soil and other substances from widely separate regions would produce it, and finally that some of them would produce it in considerably greater quantity. Strangely enough the Fleming strain and its derivative or substrains remained the best producers of penicillin for many months after the collection and testing of other members of the *chrysogenum-notatum* group began.[61]

Writing of the Fleming organism after "its emigration to America," Thom reported:

> * * * It was distributed from the laboratory in Washington by Thom and Raper to all who asked for it from 1930 onward. How many other transfers from the English-type culture collection reached America we do not know but none have come to our attention. There is one reference to Bornstein as obtaining his culture from Fleming. In a file of letters before me, we have the record of its distribution to great university laboratories, hospitals, and to manufacturing chemists who are now [1945] producing penicillin.
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> * * * * * * *

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[59] Charles Thom, "Mycology Presents Penicillin," Mycologia, vol. 37, 1945, p. 463.

[60] Sir Alexander Fleming, "History and Development of Penicillin," Penicillin, Its Practical Application, 2d ed., London, p. 14.

[61] Cf. Kenneth D. Raper, "A Decade of Antibiotics in America," Mycologia, vol. 44, January–February 1952, p. 7: "The importance of Thom's corrected diagnosis is obvious since it identified the culture with a cosmopolitan series of molds and in later years gave direction to the intensive search for more and better penicillin-producing strains."

> Roger D. Reid obtained his first culture of the Fleming organism from us in November 1930, another transfer in July 1931.[62] * * * Survey of laboratory correspondence during the period from 1933 to 1940 shows that requests for Fleming's organism came from a number of the great laboratories engaged in bacteriological research but not from the pharmaceutical manufacturers. Their immediate response to Florey's paper in 1940 suggests that they had not previously obtained the organism from other sources. In this period then whatever work was done in the laboratories using *Penicillin notatum* was not reported except the paper of Bornstein who tested penicillin against "Enterococci and other Streptococci." [63]

Bornstein, who is referred to in the above quotation, obtained cultures from Fleming in 1936, and conducted work at the Beth Israel Hospital in New York City. It also appears that the Merck Institute started preliminary investigations respecting the use of penicillium in January 1940, with cultures obtained from Beth Israel workers.[64]

These were among the earliest penicillin researches in America. They antedated publication by Florey and his coworkers of their paper "Penicillin as a Chemotherapeutic Agent," which appeared in the Lancet of August 24, 1940, and was followed by a 1941 report by Abraham, Chain, Fletcher, Florey, Gardner, Heatley, and Jennings. These British reports aroused widespread interest and requests for cultures in the United States, regarding which Thom has stated:

> Turning again to the laboratory file, requests for Fleming's organism for use by manufacturing chemists began in a letter dated September 23, 1940, another October 1, 1940. One university laboratory asked for it August 21. Was there any connection? Within a half year after the publication of the 1941 paper, laboratories and pharmaceutical houses well distributed in the United States and extending to Mexico and Brazil were supplied with transfers of the Fleming organism (144.5112.1).[65]

Not long after the work of Heatley at the Peoria laboratory began in July 1941, and practically coincident with the rise of interest of manufacturing chemists in penicillin research, the Peoria laboratory contributed the results of its past research. Florey and his associates later described these contributions as follows: * * * Moyer had the idea that corn-steep liquor, which was used extensively as a growth promoter in other fermentations, might be used instead" of a medium, troublesome to prepare, to which Heatley was accustomed. "The result was not only enhancement of growth but, as Moyer showed after later

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[62] Concerning Reid's work, Thom wrote: "His studies published in 1933, 1934, and 1935, covered the conclusion that penicillin is bacteriostatic instead of bacteriolytic, and detailed its reaction to light, gases and temperature, effects of distillation, dialysis; in the main they confirmed and extended the work of Fleming, and of the Raistrick group without going beyond the chemical and bacteriological laboratory aspects and without suggesting possibilities of development to major usefulness." (Mycologia, vol. 37, p. 464.) Other estimates are largely in agreement. Cf., e. g., National Academy of Sciences, The Chemistry of Penicillin (Editorial Board: Hans T. Clarke, John R. Johnson, and Sir Robert Robinson), Princeton University Press, Princeton, N. J., 1949 (This work will hereinafter be cited as: The Chemistry of Penicillin), p. 3: "* * * Raistrick's findings were confirmed, in general, by Reid * * * , who found in addition that the activity was lost on dialysis, and that penicillin was adsorbed on charcoal."

[63] Charles Thom, "Mycology Presents Penicillin," Mycologia, vol. 37, 1945, pp. 462–464.

[64] "The Merck Report," July 1945, p. 5. Also, according to Merck's Annual Report for 1943, "the company began its studies on Penicillin in the fall of 1939, following the initial work of Fleming and Florey in England."

[65] Charles Thom, "Mycology Presents Penicillin," Mycologia, vol. 37 (1945), p. 465.

experiments, a greatly increased yield of penicillin. Other improvements were gradually introduced, the most important of which was the substitution of lactose for glucose in the culture medium. From this laboratory, too, came the first attempt to produce penicillin in deep culture in the revolving drums used for gluconic acid and other fermentations. Before Moyer left Peoria on August 15, 1941, for a month's holiday he showed Heatley how to manage the drums. Unfortunately only two runs (with the four drums) could be made at that time. Although the yield was small * * *, penicillin was produced."[66]

Upon returning to the East from his visits to Peoria, Florey sought out the recently created Committee on Medical Research (CMR)[67] of the Office of Scientific Research and Development (OSRD), and presented his problem to the recently appointed Chairman of the Committee, Dr. A. N. Richards, professor of pharmacology and vice president in charge of medical affairs at the University of Pennsylvania. It has been stated that the result of this visit was that "Dr. Richards, * * * an experimentalist of long standing, quickly saw the possibilities inherent in penicillin; he brought to the problem the weight of his influence and his intimate knowledge of the drug houses of this country."[68] Also, the British visitors stated that "before leaving in the middle of September 1941, Florey received assurances from Dr. A. N. Richards * * * that he would see that everything possible was done to expedite production of penicillin."[69]

Early Production in England

Back in England and still anxious to extend the scope of the clinical studies of penicillin, Florey found that he was no better off than when he had left to seek help in America. The British associates have described their plight as follows: "At the time of Florey's and Heatley's visit it had been expected that some of the first penicillin supplies from American manufacturers would be made available in Oxford. However, only half a million units arrived, the

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[66] H. W. Florey et al., Antibiotics, p. 650.

[67] Cf. A. N. Richards, "Foreword" Advances in Military Medicine, edited by E. C. Andrus et al., 2 vols., Little Brown & Co., Boston, Mass., 1948, vol. I, pp. xli–xliii:

The CMR was established by executive order of President Roosevelt on June 28, 1941. The same order created the OSRD as the parent organization within which the previously established National Defense Research Committee (NDRC) and the new CMR were to be constituent agencies. Dr. Vannevar Bush was relieved of the chairmanship of the NDRC and became Director of the OSRD; he thus assumed final responsibility for the entire program of civilian scientific research and development, not only in the fields of instrumentalities of warfare but also in all fields of military medicine.

The CMR was instructed to "advise and assist the Director in the performance of his medical research duties with special reference to the mobilization of medical and scientific personnel of the Nation, * * * to recommend to the Director the need for and character of contracts to be entered into with universities, hospitals and other agencies conducting medical research activities for research and development in the field of the medical sciences, * * * [and to] submit recommendations with respect to the adequacy, progress and results of research on medical problems related to the national defense."

* * * * * * *

The President's Executive order contained no suggestions as to the sources from which the CMR should seek advisory aid. But at its first meeting on July 31, 1941, the Committee, recognizing the competence and accumulated experience of the NRC committees, decided to lean heavily on their advice. The Chairman of the Division of Medical Sciences of the NRC was elected vice chairman of the CMR; the chairmen of the eight major medical committees were appointed consultants to the CMR; and a contract between the OSRD and the National Academy of Sciences was recommended to the Director of the OSRD in amount sufficient to pay the expense incident to the meetings of the NRC committees and to the preparation and distribution of their reports. These arrangements saved invaluable time in the initiation of the work of the CMR.

[68] John F. Fulton, *op. cit.*, p. 110.

[69] H. W. Florey et al., Antibiotics, p. 650.

reasons being, in the first place, manufacturing difficulties, and in the second, with the entry of America into the war in December 1941, the appropriation by the Committee on Medical Research of all supplies for clinical trial." [70] And it has been stated in other British writings that—

> As far as securing supplies for further clinical work at Oxford went, this expedition bore little fruit, so that the Oxford workers were thrown back after all on their own resources and the small but willing help of Imperial Chemical Industries, Ltd., who supplied small amounts of dry product, and of Messrs. Kemball, Bishop & Co., Ltd., who sent a large number of 150–200-gallon lots of crude active culture fluid to Oxford by road to be processed there.
>
> With material obtained in this way a second series of cases was treated in Oxford, beginning in January 1942. The patients were treated systemically and by local application. They served to confirm fully the favorable results of the first series. These results were published by Florey and Florey in March 1943.[71]

But before this, as early, in fact, as "the beginning of 1943, sufficient supplies had been accumulated from Imperial Chemical Industries Ltd., Messrs. Kemball, Bishop & Co. Ltd., and Oxford to make it worth while for the Army to send special investigators to North Africa." Still earlier, "in April 1942, a small quantity of penicillin prepared in Oxford was offered to Major General Poole, Director of Pathology, War Office, and was dispatched to the Middle East." [72]

Though it was apparently not until October 1942 that the British Government officially took an interest in penicillin and "the Ministry of Supply set up a General Penicillin Committee," there was already in existence a Penicillin Sub-Committee of the Research Panel of the Therapeutic Research Corporation of Great Britain concerned "with the production and chemistry of penicillin." The progress reports, rendered to this committee as occasion arose, were known as the "PEN" reports; * * *. In general, the chemical information contained in these reports was not published in the scientific press, but was privately communicated to recognized workers in the field.

The developments with respect to collaboration in Great Britain following the establishment of the General Penicillin Committee have been summarized as follows:

> It was then decided that the existing Penicillin Sub-Committee should be enlarged to include other interested workers, among whom were Imperial Chemical (Pharmaceuticals) Ltd., and should continue its task of coordinating the work on production and purification to the stage fit for clinical use, reporting to the General Penicillin Committee. The name of the Sub-Committee was changed at this time to the Penicillin Producer's Conference or, as it was briefly called, the Penicillin Conference. At the same time it was arranged that the unofficial Conference of Chemists * * * should continue its function of handling information on the chemistry and structure of penicillin; the reports of this Chemists' Conference were made available to the Chairman of the General Penicillin Committee of the Ministry of Supply. [73]

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[70] H. W. Florey et al., Antibiotics, p. 651.

[71] H. W. Florey and E. P. Abraham, "The Work on Penicillin at Oxford," Journal of the History of Medicine and Allied Sciences, vol. VI, No. 3 (summer 1951), p. 310. (Dr. Mary E. Florey, wife of Dr. H. W. Florey, conducted the first extensive clinical work in connection with the local application of penicillin.)

[72] H. W. Florey et al., Antibiotics, p. 657.

[73] The Chemistry of Penicillin, p. v.

Exchange of Information Between American and British Manufacturers

The implication of the accounts by Florey and his associates of what they called "early production in England" [74] seems to be that, so far as they were aware, no members of the Therapeutic Research Corp. of Great Britain, Ltd.—Boots Pure Drug Co., Ltd.; May & Baker, Ltd.; British Drug Houses, Ltd.; Glaxo Laboratories, Ltd.; and Wellcome Foundation, Ltd.—were producing penicillin even as late as September 1942, when "Kemball, Bishop & Co., Ltd., began to take part in production." [75] Nevertheless, early in March 1942, Dr. T. B. Maxwell, official of May & Baker, Ltd., sent to George W. Merck, president, Merck & Co., Inc., the cable quoted below:

> In my capacity as Deputy Chairman, Therapeutic Research Corp., I wish to enquire whether you would be willing to approach principal American interests actively engaged in production and study of penicillin as to willingness to pool present information future data as collected and eventual United Kingdom and United States patent rights if any. Am authorized to say corporation would welcome such a step as tending to prevent overlapping of extensive programmes and possibly bring work to fruition more rapidly. Unofficial rumour here says your company Squibb and Chemical Foundation are principal American interest.[76]

Merck replied the next day, cabling May & Baker as follows:

> For Maxwell penicillin is Government project on which we and others are collaborating, but not Chemical Foundation. We shall put your proposal before authorities.[77]

The authorities were evidently consulted at least promptly enough for Richards to have reached a decision by March 12, 1942, when he wrote to Merck & Co., Inc. (in part):

> I can say at once that the Committee on Medical Research would have no objection to the distribution of such information as the American investigators possess concerning penicillin to the members of the Therapeutic Research Corporation of England. The question is to what extent the Americans will agree to the suggestion.
>
> As I understand it, Merck and Squibb are working in close collaboration and are sharing information and experience. Thus far, this represents the extent of American pooling. I judge that it would be wholly proper for your two firms to offer to exchange information with the British.[78]

Subsequent to the initial exchange of cables just noticed, informal arrangements, evidenced by cables, were entered into by Merck and Squibb with certain

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[74] H. W. Florey et al., Antibiotics, p. 651.

[75] H. W. Florey et al., Antibiotics, p. 651. Sir Alexander Fleming is one authority for the scarcity of penicillin in the summer of 1942. "The first patient I ever treated with concentrated penicillin was a patient in St. Mary's Hospital, London, a friend of mine * * *. I tested the sensitivity of the streptococcus to crude penicillin—it was sensitive. But I had no concentrated penicillin; in fact there was none in the world then except a little which Florey had at Oxford. Florey was good enough to supply me with, I think, his whole stock * * * It was a most dramatic recovery." ("Antiseptics Old and New" (A Mayo Foundation Lecture, given July 16, 1945), Proceedings of the Staff Meetings of the Mayo Clinic, vol. 21, No. 4 (February 20, 1946), pp. 74–75.)

[76] May & Baker, Ltd., to George W. Merck, March 5, 1942, records of OSRD, NA, RG 227.

[77] George W. Merck to May & Baker, Ltd., March 6, 1942, records of OSRD, NA, RG 227.

[78] A. N. Richards to J. C. Woodruff, Merck & Co., Inc., March 12, 1942, NA, RG 227.

organizations associated with the Therapeutic Research Corp.;[79] and, following the agreement of September 1943, for collaboration among Merck, Squibb, and Pfizer, the last-named of these companies also became a party to the arrangements, which continued in effect until February 22, 1945.[80] After becoming commercial contractors under the OSRD's penicillin synthesis program, Merck and Squibb turned over to OSRD various reports in the "PEN" series, identified above, relevant to the research they had undertaken.[81]

First Efforts of the Office of Scientific Research and Development To Obtain Production of Penicillin

In his "Foreword" to Advances in Military Medicine, after having said that "Florey's conversations with the Chairman and other members of the CMR [Committee on Medical Research] led them to share his convictions [concerning the potentialties of penicillin] and to decide to attempt the promotion of the effort he so ardently desired," Richards outlined the Committee's first steps toward enlisting commercial support as follows:

> * * * In October 1941, a meeting was held in Dr. Bush's office to discuss the possibility of a cooperative effort to produce penicillin in quantity. Present were Dr. Bush, the Chairman and Vice-Chairman of the CMR,[82] the Chief Mycologist of the Department of Agriculture,[83] the Chairman of the Division of Chemistry of the NRC,[84] and the scientific directors of four large Eastern pharmaceutical manufacturing houses.[85] * * *[86]

In his testimony at the Senate hearings on science legislation in 1945, some of which has already been noticed, Richards spoke of "all four companies agreeing to put their research teams or fractions of them on the problems. As a result," he said, "we began to get a trickle of a supply of penicillin during the early months of 1942."[87]

Regarding Richards' assurances to Florey in September 1941, "that he would see that everything possible was done to expedite production of penicillin," Florey and his associates, who had had firsthand experience of production problems, commented some years later:

> * * * Just how formidable its preparation was at that time can best be illustrated by a small calculation. The penicillin content of crude brew at Oxford with the medium and strain of fungus then in use was about 1 to 2 units per ml. Sixty percent of this might be lost during extraction and purification, so that on the evidence then available every case of severe sepsis

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[79] Cf. The Economist (London), February 19, 1944, p. 238: "* * * it cannot be forgotten that when the Therapeutic Research Corp. was set up, combination in marketing seemed to be as important an objective for it as collaboration in research."

[80] Records of OSRD, NA, RG 227.

[81] The Chemistry of Penicillin, pp. v, 1056, 1063.

[82] Respectively Dr. Richards and Dr. Lewis H. Weed.

[83] Dr. Charles Thom.

[84] Dr. William Mansfield Clark,

[85] The companies represented were Merck & Co., Inc., E. R. Squibb & Sons, Chas. Pfizer & Co., Inc., and Lederle Laboratories, Inc. (then a wholly owned subsidiary of American Cyanamid Co.). Merck and Pfizer were producers of fine and medicinal chemicals. The four companies listed above were respectively represented by Dr. Randolph T. Major, Dr. George A. Harrop, Mr. Jasper H. Kane, and Dr. Y. SubbaRow.

[86] A. N. Richards, "Foreword" to Advances in Military Medicine, edited by E. C. Andrus et al., 2 vols., Little. Brown & Co., Boston, Mass., 1948, vol. I, p. li.

[87] Senate hearings on science legislation, 1945, pt. 3, pp. 461–462.

> might need the brewing and processing of as much as 2,000 liters of medium. It appeared therefore that the cost would be high and the number of cases that could be treated by parenteral injection would be few.[88]

Following the meeting of October 8, 1941, referred to earlier, Thom had undertaken a tour on behalf of the Committee on Medical Research. He was to bring back impressions concerning the facilities, competence, progress, and attitudes of the companies whose help had already been solicited. In addition, it was desired that he attempt to judge the interest in penicillin on the part of several other companies. Among these, it was hoped that he might be able to enlist the effort of at least one company smaller than those whose representatives had lately conferred with OSRD. It was hoped that such a smaller company could be found which had fermentation facilities and personnel with sufficient training in "culture work" to enable it to produce penicillin for clinical use and chemical study.

On October 20, 1941, Thom wrote from Beltsville, informing Richards of what had been learned on the trip. At least six commercial companies, including manufacturers of fine and medicinal chemicals as well as pharmaceutical houses, were reported by Thom to have manifested varying degrees of interest in the production of penicillin by fermentation. The word from Peoria was particularly encouraging: "Moyer has been able to increase the experimental yield of Penicillin to three times what Heatley could produce by his methods." The members of the staff who had been working on penicillin were interested; and while they realized that the regional laboratory was "not equipped for large-scale production of penicillin," they believed that the laboratory could contribute to "the research work necessary," if support were provided for such a program as was outlined in their recommendations. This program included:

> 1. Further experiments to increase the yield from Fleming's organism.
> 2. Improvement and standardization of the assay method to determine yield and effectiveness.
> 3. Search of a large number of organisms for one capable of producing a satisfactory yield. * * *
> 4. Further study of "drum" method of fermentation is very desirable.[89]

The responsiveness of Merck to the OSRD proposals has already been seen in the report of the meeting of October 8, 1941, incorporated above. Opinions were exchanged among the companies regarding the plans for cooperation proposed by OSRD. For instance, on October 13, 1941, Dr. Major of Merck wrote to Pfizer's "Mr. Kane concerning the penicillin conference held on October 8 in Washington"; and on October 14, Pfizer had had a telephone call from George W. Merck, president of Merck. In a letter to Merck dated October 15, 1941, John L. Smith, vice president of Pfizer, set forth Pfizer's position. A copy of this letter was furnished to Dr. Richards. This letter is quoted almost in full below:

> Some months ago we were approached by Dr. Dawson of Columbia University regarding possible assistance which we might give in providing penicillin for clinical use and other studies. At about the same time Dr. Anderson of E. R. Squibb & Sons called me and asked whether, because of our large scale work with molds, we might be in a position to provide them with liquors containing penicillin. Shortly thereafter you spoke to me about the same matter and Dr. Major also telephoned me regarding it.

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[88] H. W. Florey et al., Penicillin, pp. 650–651.

[89] Charles Thom to A. N. Richards, October 20, 1941, records of OSRD, NA, RG 227.

It appears that the penicillin problem is of great interest and importance to the national defense program, and we would be glad to collaborate with other companies in attempting solution of the problem if we are in a position to be useful. However, we at the present time know very little about the characteristics and deportment of the organism used to produce penicillin, or the conditions under which it will give what are considered to be satisfactory results, and before we commit ourselves to actively collaborate in this work we must determine through experimentation within our own laboratory what effect the introduction of the penicillium (the organism used for preparing penicillin) has on other fermentation work in which we are already engaged. It has been our experience that the invasion of other mold organisms into our established fermentation work may result in dire consequences. Therefore, we must be sure that the hazards involved are controllable. Our position in this respect has been made clear to all who approached us.

During the past few weeks our laboratories have been doing work with *Penicillium* in a modest way and a considerable number of samples of liquor have been sent to Dr. Dawson for evaluation. Our work so far indicates that many essential factors are still unknown, such as the best composition of the media, the conditions under which penicillin is produced in satisfactory yield, and the stability of the product after it has been produced in the liquors. The absence of information on these points leads me to believe that research work should be undertaken to establish these essential factors before large scale production is attempted.

As I have indicated above, we are not in a position to state whether it would be possible to collaborate in this work until we have demonstrated to our own satisfaction whether uncontrollable hazards are involved for us. Nevertheless, in view of the apparent importance of the work, we would be glad to attend a meeting such as Dr. Major suggests to discuss the question of collaboration so that the scope and terms of the collaborative effort might be agreed upon while we are conducting work to determine the possibility of our participation.[90]

A meeting concerning penicillin, attended by representatives of Lederle Merck, Pfizer, and Squibb, was held in New York on November 11, 1941; but what was reported concerning it to OSRD was scarcely definite enough to be greatly encouraging.

Still entertaining understandable reservations about the Penicillia, Pfizer, by its vice president, John L. Smith, wrote again to Richards on December 9, 1941, saying (in part):

I might say that this company is making moderate quantities of penicillin liquor weekly, part of which are sent to Dr. M. Henry Dawson of Columbia University for evaluation and study, and part are being used in our own laboratories in an effort to determine the characteristics of penicillin, a satisfactory method of extraction, and possibly its structure.

We are engaged in commercial fermentation work, and *Penicillium* is one of the organisms which very often contaminate these processes and create much difficulty. For this reason we must feel our way cautiously and endeavor to establish whether or not the *Penicillium* organism, used for the production of penicillin, may adversely effect [sic] the fermentations which we are now conducting, if the production of penicillin were undertaken in our plant. The work we have done so far has not created serious

[90] John L. Smith to George W. Merck, October 15, 1941, with copy to A. N. Richards, records of OSRD, NA, RG 2297.

> problems for us, but we have worked on entirely too modest a scale to be sure of the effect which the cultivation of *Penicillium* organisms in our plant may bring with it. Therefore, while we are anxious to cooperate with other companies in a study of the penicillin problem, the degree to which this can be done is dependent upon the effect this work will have on other fermentations now being conducted by us.
>
> I wish to assure you that if a satisfactory collaborative procedure can be worked out between the companies who appear to be in a position to contribute to the penicillin problem, we will give our enthusiastic support to such an endeavor.[91]

During the latter part of December 1941, Coghill had visited the Merck, Squibb, and Pfizer plants on behalf of the Committee on Medical Research, but in trying to compare the activities of the companies had encountered various difficulties. One of the most serious of these was the use of different assay methods, which made it impossible to estimate relative success in recovery.

In connection with assay methods, Richards wrote on January 24, 1942, to Dr. Perrin H. Long, Chairman of the Committee on Chemotherapeutic and Other Agents of the National Research Council:

> If you are not already aware of it you should know that arrangements are being made whereby Dr. R. D. Coghill of the Northern Regional Laboratory, United States Department of Agriculture at Peoria, Ill., will undertake the assay of various preparations of penicillin which will be submitted to him by the different manufacturers who are busy with the production of that substance. It seems clear that a uniform method should be established and that those who are engaged in clinical testing should know the potency of the product which they are using.
>
> Nothing as yet has been arranged concerning toxicity testing. I understand that both Merck and Squibb are subjecting their preparations to animal test and shall communicate with them in the hope of discovering where and by whom such testing can be done routinely.[92]

"Unexpected difficulties have been encountered in the production of the substance," Richards said further, "but they are being overcome and I think that we can expect, shortly, to have enough to be of interest to your Committee." [93] As it turned out, however, it was not until March that penicillin was administered to the first patient to receive any officially—i. e., pursuant to the OSRD program of clinical investigation.[94] "* * * "in May 1942, Dr. Long entered the Army," [95] and thus he had little responsibility for the clinical testing of penicillin.

The plans for clinical investigation just referred to had been projected in December 1941, when the OSRD Committee on Medical Research requested

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[91] John L. Smith to A. N. Richards, December 9, 1941, records of OSRD, NA, RG 227.

[92] A. N. Richards to Perrin H. Long, January 24, 1942, records of the OSRD, NA, RG 227.

[93] A. N. Richards to Perrin H. Long, January 24, 1942, records of OSRD, NA, RG 227.

[94] Cf. Dr. John F. Fulton, "Penicillin, Plasma Fractionation, and the Physician," the Atlantic Monthly, September 1945, p. 110: "The first patient in this country to receive penicillin developed under the OSRD program was the wife of a member of the Yale faculty who had had a progressive streptococcus septicemia with temperatures ranging 104° to 106° during the 4 weeks of her illness. She was near death when she received her first injection of penicillin on Saturday afternoon, March 14, 1942. Within 2 hours her temperature had dropped to 99° and, whereas she has had an average of 200 organisms in each cubic millimeter of her blood (which had remained untouched by the sulfa drugs), within 24 hours of her first dose of penicillin her blood stream had become sterile. Although the penicillin available in 1942 was not yet pure, it was highly effective. The patient recovered and has been entirely free of trouble ever since."

[95] John F. Fulton, op, cit., p. 110.

the National Research Council's Committee on Chemotherapeutic and Other Agents "to initiate and coordinate an extensive study of the therapeutic use and limitations of penicillin." Regarding this study Richards wrote:

> This study was carried on with extraordinary competence in selected clinics, and by March of 1943 the results of treatment of 200 cases with penicillin were available. They were so impressive that in April of that year, by arrangement with the Surgeon General of the Army, one of the civilian investigators under the CMR was invited to conduct a study of the effects of penicillin in the treatment of compound fractures and osteomyelitis in wounded soldiers from the Pacific theater at the Bushnell General Hospital. The success of this study led to the initiation of programs of study and indoctrination in Army hospitals, which were antecedent to the general adoption of penicillin throughout the Army medical services.[96]

The foregoing has described only the highlights of the earlier clinical investigation of penicillin during World War II. Dr. Chester S. Keefer, who was in charge of the program of clinical investigation throughout almost its entire life, has attributed much of the credit of the OSRD clinical investigation program to private hospitals and physicians, as follows:

> Progress in the production of penicillin was at first slow. The first small quantities of penicillin became available in this country in the spring of 1942, but by the end of that year only enough drug had been produced to treat 100 patients.
>
> The difficulty of producing the drug in significant quantities early led to a general agreement between the producers of penicillin and the Committee on Medical Research that as long as the supply of the drug remained limited, the entire production should be assigned to one agency for clinical testing. The purpose of this action was to insure that the maximum amount of information about the clinical use and effectiveness of the penicillin could be obtained from the small supply of drug that was being produced. The agency selected by the Committee on Medical Research of the Office of Scientific Research and Development for this purpose was the Committee on Chemotherapeutics and Other Agents of the National Research Council. From the spring of 1942 until January 1943 the entire supply of penicillin that was produced by several manufacturers for clinical testing was turned over to the Committee on Medical Research for this purpose without cost.
>
> Beginning on January 1, 1943, and extending to December 31, 1945, the Office of Scientific Research and Development purchased the penicillin and entered into a contract with the Massachusetts Memorial Hospitals under which the hospitals through their responsible investigator were to collect information concerning penicillin under the direction of the Committee on Chemotherapeutics and Other Agents of the National Research Council and the Committee on Medical Research.
>
> In carrying out this program, penicillin was assigned to the hospitals by the Office of Scientific Research and Development for distribution to accredited investigators and individual physicians throughout the country for use in the treatment of diseases in which the Committee on Medical Research had requested that information be obtained regarding the clinical effectiveness of penicillin. In return for being provided with penicillin without charge to him or to his patients, each investigator agreed to furnish

[96] A. N. Richards, "Foreword" to Advances in Military Medicine, edited by E. C. Andrus et al., 2 vols., Little, Brown & Co., Boston, 1948, vol. I, pp. li–lii.

the Committee with detailed reports of the cases in which the drug was used.

From the spring of 1942 until July 16, 1943, the supply of penicillin remained so small that it was possible to furnish penicillin only to a small group of "accredited investigators" who were selected by the Committee on Chemotherapy. These accredited investigators were all recognized experts in the fields of chemotherapy and infectious diseases. With the limited amounts of penicillin that were allotted to them, they studied and reported on the action of the drug in patients with severe staphylococcic infections and to a very limited extent in patients suffering from infections caused by other gram-positive cocci that were not responding to sulfonamide therapy.

After July 16, 1943, all of the penicillin produced in the United States was placed under allocation order by the War Production Board, and the increased production of penicillin at about this time made it possible to extend greatly the clinical trial of penicillin. At this time it became possible to supply the drug to individual physicians throughout the country who had under their care patients with infections concerning the action of penicillin in which the Committee on Medical Research had requested that information be obtained. At first the number of diseases that could be studied and the number of patients who could be treated under this program remained small. As the production of penicillin increased rapidly from month to month during the latter part of 1943 and the early part of 1944, it was possible to provide penicillin for the treatment of all patients with serious infections in whom bacteriologic studies indicated that the use of penicillin would be of value.

In May 1944, the production of penicillin in this country was sufficiently great and the needs of the Armed Forces of our country and allies were being met so that limited sale of the drug through hospitals was permitted by the War Production Board. After this date the distribution of penicillin under contract with the Office of Scientific Research and Development and the Massachusetts Memorial Hospital was limited to special investigators who were studying the use of penicillin in certain conditions in which the Committee on Medical Research requested that more information be obtained. This program continued on a small scale until the expiration of the contract on December 30, 1945.

In the period of slightly less than 4 years during which this program of the study of penicillin was in operation, reports on the use of penicillin in a total of 10,838 patients were submitted to the Committee on Chemotherapeutics and Other Agents. At frequent intervals, the reports were analyzed and the resulting information was transmitted to the Committee on Medical Research, which in turn passed the information on to the armed services and other interested agencies.

When the program outlined above was concluded at the end of 1945, it was felt that a more detailed analysis of the 10,838 case reports than was possible during the active period of the program would produce information that would be of significant value to an understanding of the action of penicillin. Accordingly a new contract was issued by the Office of Scientific Research and Development for this purpose. When this contract expired on June 30, 1946, the material from the case reports had been put in such a form that it could be readily analyzed. The actual analysis was then undertaken with the help of a grant-in-aid from the United States Public Health Service.[97]

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[97] Donald G. Anderson and Chester S. Keefer, "The Therapeutic Value of Penicillin, a Study of 10,000 cases," J. W. Edwards, Ann Arbor, Mich., 1948, pp. v–vii.

Expansion of Penicillin Research at the Northern Regional Research Laboratory, Peoria

During December 1941, the Committee on Medical Research was concerned with several problems relating to penicillin. On December 17, it held in New York its second meeting[98] with representatives of the four companies it hoped would undertake production of sufficient quantities of penicillin for comprehensive clinical evaluation; it made arrangements with the Committee on Therapeutic and Other Agents of the National Research Council for the organization and conduct of clinical tests to be carried out when enough of the drug should become available, and it decided to finance at Peoria an enlarged research program devoted to penicillin. Heatley left Peoria in mid-December 1941,[99] and spent the next 6 months in the employ of Merck & Co., Inc., at Rahway, N. J.

What had already been accomplished by the staff at the Northern Regional Research Laboratory led the Committee on Medical Research to make certain that there should be no curtailment of the work being done on penicillin at that laboratory and to provide for some expansion. This was accomplished by means of an OSRD contract with the Bradley Polytechnic Institute in Peoria, under which, beginning on February 1, 1942, it provided services in the Fermentation Division. These services were performed "with Dr. Coghill as the responsible investigator. The contract covered a period of 6 months and was subject to renewal. In announcing it, Dr. Richards expressed the hope that the plan of work would include a standardization of the method of assay that could be used by producers of penicillin. This was subsequently done."[1]

Since the early months of 1942, the Committee on Medical Research had undertaken to assist companies producing or preparing to produce penicillin by recommending to the War Production Board the granting of the requisite priorities.[2] The War Production Board appears to have been slow in acting upon these recommendations, for after a series of instructive letters extending over approximately a year, Dr. Richards seems still to have felt a need to convince the WPB of the merits of penicillin.

Thus, on March 18, 1943, writing to the WPB in support of an "application * * * being made by the Chester County Mushroom Laboratories for certain apparatus" to be used in "developmental research" looking toward the production of penicillin, Richards had explained why he wished "to indorse their application in the strongest terms and to express the hope that action upon their request [might] be expedited":

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[98] It is of interest that among the references cited as of record in the file of U. S. Patent No. 2,443,989, "Method for Production of Penicillin," Andrew J. Moyer, Peoria, Ill., assignor to the United States of America as represented by the Secretary of Agriculture, there appears the following: "Moyer and Heatley, a paper distributed to Merck, Squibb, Pfizer, Lederle, and OSRD in New York City [sic] on December 17, 1941."

[99] Up to this time Heatley's support had been provided by the Rockefeller Foundation, which had extended the grant on which he had accompanied Florey to the United States. It has been mentioned previously that Heatley was responsible for the assay method used by the Oxford collaborators. But it should not be overlooked that he supervised production of the penicillin used in the investigations reported by the Oxford workers in 1941. Cf. E. P. Abraham, E. Chain, C. M. Fletcher, H. W. Florey, A. D. Gardner, N. G. Heatley, and M. A. Jennings, "Further Observations on Penicillin," Lancet 2, August 16, 1941, p. 188: "N. G. Heatley devised the assay method and developed and supervised the production of penicillin."

[1] E. C. Andrus et al., Advances in Military Medicine, 2 vols., Little, Brown & Co., Boston, 1948, vol. II, p. 725.

[2] A. N. Richards, Foreword to Advances in Military Medicine, edited by E. C. Andrus et al., 2 vols., Little, Brown & Co., Boston, Mass., 1948, vol. I, p. —.

> You may be aware that one of the most promising developments in the field of military medicine which has been taking place during the past 2 years is the study and production of a substance known as penicilin derived from cultures of a common mold *Penicillium notatum.*
>
> This substance, at present produced in small quantities, has been subjected to extensive clinical tests and has been shown conclusively to possess unique value in the treatment of blood stream infections, local infections, such as occur in connection with wounds and burns, and in certain venereal diseases. It is becoming daily more certain that in some conditions its value as a medicament is far greater than that of the sulfonamide substances.
>
> There is no question in the minds of those who are most familiar with this matter that when the substance is available in quantity it will be urgently required by our Armed Forces. * * *[3]

Further light on the state of affairs with respect to penicillin at about the end of March 1943 can be obtained from the following letter, written by Richards to Coghill on April 9, 1943:

> I have your letter of March 26 and am glad to know that the Pfizer Co. is willing to disclose certain details of their method for recovery of penicillin. I hope that the information can go to all of those who are now struggling to produce it.
>
> A fine opportunity has presented for further testing of the clinical usefulness of penicillin in Army casualties. There are some 1,500 wounded men from the Pacific area now undergoing treatment at the Bushnell General Hospital, Brigham City, Utah. At the request of our committee the Surgeon General authorized Dr. Champ Lyons, of Boston, to proceed to the Bushnell Hospital to undertake the supervision of the use of penicillin in the treatment of compound fractures, osteomyelitis, and such other injuries as may be encountered. He is using about a million units a day and the conditions which have been arranged for him are said to be practically ideal. I hope soon to be able to have some sent to England and to North Africa and at the same time to encourage increased production.
>
> I think many times of the encouragement which you gave me to believe that your group is well on its way toward completeness of knowledge concerning the constitution of penicillin. I hope you are not encountering too many disappointments and should be greatly interested to know more of your progress.[4]

Root's response was prompt; and on May 7, 1943, Richards announced to American Cyanamid, Merck, Pfizer, and Squibb: "At the request of the Director of the Office of Scientific Research and Development, Mr. Elihu Root, Jr., has consented to act as adviser to the Committee of Medical Research in relation to the interests of the Committee in the production of penicillin." Continuing, he wrote:

> That substance, apparently unique in its power to combat bacterial infections to which wounded men are subject, has become a matter of intense interest in the medical aspects of the war effort. For nearly a year past, the Committee on Medical Research has been encouraging efforts looking toward the production of penicillin and has sponsored Government

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[3] A. N. Richards to William J. McManus, WPB, March 18, 1943, records of OSRD, RG 227.

[4] A. N. Richards to Robert D. Coghill, April 9, 1943, records of the OSRD, NA, RG 227.

> contracts for investigations of its action. From these investigations it has become apparent that plans must be made for production sufficient to satisfy greatly increased demand.
>
> Mr. Root's assistance is being invited in the construction of the broad program which is necessary. He wishes to obtain information from several interested companies with respect to present production and plans for expansion.

Richards hoped that it would be found "possible to authorize arrangements" that would give Root the information desired from each company.[5]

Regarding the interest of potential manufacturers wishing to engage in penicillin production, Dr. Coghill stated about 1 year later that:

> By July 1943, the combined efforts of the original pioneering companies and the clinicians had well established the value of penicillin, and much unfortunate newspaper publicity had served to whet the public appetite. Literally scores of potential producers wanted to get on the bandwagon. * * * Many of these potential producers had been quietly carrying on research on production methods and knew what they were about. These were welcomed into the field (at least on the part of the Government), as it was obvious that prodigious amounts would be needed for the Army, Navy, and civilian population.[6]

War Production Board Undertakes Responsibility for Expanding Penicillin Production

According to Fred J. Stock, Chief, Drugs and Cosmetics Branch, Chemicals Bureau, War Production Board:

> Early in 1943 the Committee [on Medical Research] began to report the results of its clinical investigations of penicillin. The results were made available to the military, who were enthusiastic about this potent antibiotic agent.[7]

Matters relating to the penicillin production program were discussed in detail at a meeting on August 31, 1943. The main points considered, and the decisions reached, are reported in the following paragraphs from an account of the discussion appearing in the records of the OSRD:

> On Tuesday, August 31, there was a meeting at Dr. Bush's office, attended by Messrs. Morgan, Stock, Raynolds, and Brown of the Chemicals Division of the War Production Board; Dr. Bush, Mr. Elihu Root, Jr., Dr. Richards, of the Committee on Medical Research; Mr. Carroll L. Wilson, and Mr. R. E. Waterman. It was agreed that primary responsibility was on the War Production Board for expanding the production of penicillin, determining the type of production by various producers, surface or deep fermentation, providing financing for the producers where necessary, issuing necessary priorities for materials required by producers for plant construction and operation, making arrangements for the disclosure of necessary technical

[5] A. N. Richards, May 7, 1943, to W. B. Bell, president, American Cyanamid Co.; George W. Merck, president, Merck & Co., Inc.; John L. Smith, vice president, Chas. Pfizer & Co., Inc.; Carleton H. Palmer, chairman of the board, E. R. Squibb & Sons. Records of OSRD, NA, RG 227.

[6] Robert D. Coghill, "Penicillin, Science's Cinderella," Chemical & Engineering News, vol. 22, No. 8 (April 25, 1944), p. 590.

[7] Journal of the American Pharmaceutical Association, Practical Pharmacy Edition, vol. VI (April 1945), p. 110.

information relating to techniques of production on terms just to the producers, and dealing in some just and effective manner with patent rights relating to methods and apparatus for production of penicillin by the present means (surface and deep). Mr. Morgan indicated that WPB might appoint an industry advisory committee on penicillin, composed of representatives of those now producing or negotiating to produce material, such a committee to follow the general pattern of industry advisory committees appointed by WPB. He indicated that OSRD might be invited to send a representative to meetings of such a committee or its subcommittees at such times as problems affecting OSRD's phase of the job require consideration or would be benefited by obtaining the suggestions and opinions of the producers.

It was agreed that primary responsibility was on OSRD for organizing and promoting research on the synthesis of penicillin, for financing such research, for arranging for necessary interchange of technical information among those engaged on research on the synthesis, for working out with such firms or institutions equitable arrangements concerning patents based on such research and secrecy orders relating to such patents, for conducting the nonmilitary clinical research on pencillin, for distributing penicillin allocated for research among the various groups engaged on synthesis work and allocating that assigned for clinical testing among hospitals engaged in the general program sponsored by OSRD, and for dealing with representatives of Allied Governments in regard to disclosure of information relating to research on synthesis or information relating to the clinical testing program.

It was considered desirable that all research on the synthesis of penicillin be carried forward under OSRD contracts. The penicillin allocated for research on synthesis might be limited to those contractors of OSRD engaged in research on the synthesis. If it did not appear practicable to bring all research on synthesis under OSRD contract, some arrangement should be made with those firms to whom penicillin is allocated for research on synthesis and who do not operate under OSRD contract in order that they may be obliged to handle resulting patent rights in a reasonable manner which might mean licensing certain other firms at reasonable royalties.

It was agreed that the present arrangement under which the monthly production of penicillin is allocated among the Army, Navy, United States Public Health Service, and OSRD be continued since it seemed to function satisfactorily. Penicillin allocated for research, whether it be research on synthesis or clinical testing, should be to the OSRD.[8]

The amount of penicillin produced in 1944 and the producers is revealed in the following WPB compilation. (Appendix table 1, p. 331.)

More than half of the American plants appear to have been operated by members of the American Drug Manufacturers Association, referred to by its president at its annual meeting held in 1943 as "an association comprised of manufacturers of most of the prescription products in the country." Its members who had embarked upon penicillin production were: Abbott, Cutter, Heyden, Lederle, Lilly, Merck, Pfizer, Upjohn, Reichel Laboratories, Squibb, Hoffmann-LaRoche, Winthrop, and Parke, Davis. Four of these—Abbott, Lilly, Squibb, and Parke, Davis—were members of the group characterized by Fortune in 1940 as "The Big Five of Ethicals." [9] Each of these four was a "long-line"

[8] "Memorandum of Meeting for Discussion of Penicillin Program." by C. L. Wilson, September 10, 1943, records of OSRD, NA, RG 227. See ch. I, p. 43, also.

[9] Fortune, August 1940 ("Abbott Laboratories"), p. 66.

APPENDIX TABLE 1.—*Penicillin: Actual deliveries—medicinal grades, 1944*

[Dec. 1, 1944. Unit: Million Oxford Units]

Company	January	February	March	April	May	June	July	August	September	October	November (estimated)	December (estimated)
Abbott	711.95	1,222.4	2,902.2	2,810.8	5,457.0	2,818.6	2,417.0	3,620.0	1,949.5	2,415.5	2,000	1,000
Ben Venue	4.10	127.4	302.8	992.7	438.9	859.0	600.0	1,250.0	1,815.0	1,825.0	2,000	2,000
Cheplin	0	0	0	11.64	18.7	6.4	0	0	304.4	2,007.2	6,000	7,000
Commercial Solvents	31.79	14.205	11.68	9,143.0	17,634.0	23,107.4	22,739.9	32,163.9	34,570.0	39,975.0	60,000	50,000
Cutter	0	5.0	39.0	180.3	325.5	853.8	2,384.1	1,845.0	1,419.0	1,988.0	2,250	2,000
Harrower	0	0	0	0	6.7	0	0	0	0	0	55	0
Heyden	0	0	0	50.0	21.0	---	---	---	---	9,819.0	18,000	18,000
Hoffmann-LaRoche	44.7	81.0	45.5	149.6	110.0	132.0	143.5	120.0	130.0	420.0	1,230	1,500
Lederle	131.2	267.7	163.3	119.0	249.0	1,119.0	2,030.0	5,200.0	7,840.3	5,896.7	6,000	6,000
Lilly	433.9	1,500.0	3,230.0	4,286.9	3,947.5	3,896.4	2,512.0	2,362.0	1,950.0	2,004.5	4,000	3,000
McKesson & Robbins[1]	0	19.6	23.8	43.0	36.0	66.6	20.0	66.2	34.3	31.8	45	40
Merck	3,161.22	2,444.12	2,923.254	5,003.11	7,118.4	5,086.9	3,387.65	4,702.3	7,321.5	6,485.45	8,000	12,000
Merck (Allied)	0	29.2	0	210.1	50.0	142.1	0	0	227.4	0	0	0
Parke, Davis	30.4	29.5	74.56	169.325	91.9	45.7	218.4	258.85	15.1	10.2	85	0
Pfizer	3,981.44	5,074.43	9,635.5	32,710.08	48,014.4	71,763.6	73,002.4	86,271.7	88,399.7	89,550.0	100,000	100,000
Reichel	3,100.0	2,496.0	2,262.8	650.0	1,700.0	1,826.0	1,710.2	1,350.0	2,350.0	5,704.5	6,400	7,000
Schenley	10.0	62.3	19.95	91.57	.8	15.0	10.7	1.3	396.0	2,560.0	4,000	6,000
Schering	0	0	0	0	0	0	15.0	11.0	16.5	30.0	35	30
Squibb	614.89	2,226.3	1,767.3	5,673.575	9,352.0	12,621.0	15,514.1	18,991.5	30,001.0	36,150.0	40,000	55,000
Sharp & Dohme	1.14	5.75	29.6	63.7	152.1	441.0	375.0	384.4	363.8	335.1	400	400
Upjohn	71.8	389.2	693.8	1,100.4	407.3	3,199.5	2,500.625	2,500.0	3,015.4	2,950.0	3,000	2,500
Winthrop	222.3	218.025	196.95	529.6	558.8	389.3	410.15	0	500.0	500.0	500	500
Winthrop (Heyden)	0	0	35.0	59.1	70.0	460.0	1,740.0	2,320.0	12,265.2	5,867.0	0	0
Total	12,550.83	16,212.13	24,356.994	64,047.5	95,760.0	128,849.3	131,730.725	163,418.15	194,884.1	216,524.95	264,000	273,970

[1] "McKesson & Robbins, a company not usually considered in the group of penicillin manufacturers, is producing more penicillin than several firms represented on the commitee, although it has received no priorities assistance. Its output will be allocated along with the other production." (Summary, meeting of Penicillin Producers Industry Advisory Committee, December 16, 1943, records of WPB, NA. RG 179.)

In addition there were relatively small quantities of nonmedicinal grades produced and allocated for processing each month. This material was reallocated as medicinal grades in subsequent months.

Source: Biologicals and Parenteral Solutions Unit, Drugs and Cosmetics Branch, Chemicals Bureau, WPB.

pharmaceutical house, as also was Upjohn. Of the "principal ethical pharmaceutical houses," 12 in number, named by Business Week in July 1943,[10] the following were among the operators of penicillin plants listed above: Abbott, Hoffmann-LaRoche, Lederle, Lilly, Parke, Davis, Squibb, Upjohn, and Winthrop.

Some of the companies were also members, active or associate, of the American Pharmaceutical Manufacturers' Association. Abbott, the Calco Chemical Division of American Cyanamid, and Hoffmann-LaRoche were active members in 1943; Winthrop and the United States subsidiary of Ayerst, McKenna & Harrison, Ltd., became active members in 1944.[11] Merck, Pfizer, and Heyden, primarily manufacturers of fine and medicinal chemicals, were associate members.

Many relationships, ranging from competition in the production and sale of the same products to purely commercial supplier relationships already existed among the companies selected for participation in the penicillin program. Those who were producers of medicinal and fine chemicals were suppliers to the more strictly pharmaceutical manufacturers.[12]

The major pharmaceutical manufacturers were active in the vitamin business, and for their dosage forms purchased at least some bulk vitamins, suppliers of which included American Cyanamid, Merck, and Pfizer. In the field of patent relationships, several of the penicillin producers were parties to the "Sulfathiazole Agreement" (July 11, 1940), which had terminated interference proceedings involving nine parties and three interferences.[13]

A number of the companies also were licensees of the Wisconsin Alumni Research Association under the Steenbock patents. Parke, Davis was a pioneer manufacturer of biological products. Lederle Laboratories, Inc., had formerly been the Lederle Antitoxin Laboratories. Abbott, Cheplin, Cutter, Lilly, Reichel, Squibb, and Upjohn also had backgrounds in biologicals, as did both the Canadian companies.

Fermentation experience was possessed by only some of the companies, and among them it varied considerably as to length and kind. In 1938 Merck had "established a fellowship" in Waksman's "laboratory for the study of citric and fumaric acid production by submerged fermentations"; it had worked on actinomycin and streptothricin;[14] and of all the companies it seems to have been interested longest in penicillin. Schenley's familiarity with fermentation was based on its long experience as a distiller. "Commercial Solvents Corp. was born of intensive World War I research in explosives and earned distinction as the pioneer producer of acetone and butanol by fermentation processes."[15] In 1943, the company was said to be "principally engaged in the manufacture of organic chemicals (chiefly the basic solvents) by fermentation of grains and molasses," and its operating "both by biological and by strictly

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[10] Op. cit., July 10, 1943, p. 6. (Business Week's mention of pharmaceutical companies was not in connection with penicillin.)

[11] "The active membership shall consist of manufacturers of pharmaceutical, biological, and other products used in the medical and allied professions." (American Pharmaceutical Manufacturers' Association, Proceedings, Annual Meeting, 1942, p. 253.)

[12] Fortune, June 1947, "Merck," p. 105. This article referred to Abbott, Lilly, Squibb, and Parke, Davis as "Merck's best customers."

[13] The parties to that agreement who also were penicillin producers were Merck (who received the patent), Cyanamid, Lilly, Squibb, and Winthrop.

[14] Selman A. Waksman, My Life With the Microbes, Simon & Shuster, New York, 1954, pp. 337 ff.

[15] Williams Haynes, American Chemical Industry, vol. VI (The Chemical Companies), p. 85.

chemical processes" was said to differentiate it from "most chemical manufacturers." [16] One of its profitable byproducts was riboflavin, vitamin B_2.

Pfizer's experience with fermentation was long and extensive. Outlining Pfizer's "basic position" in 1943, Merrill Lynch, Pierce, Fenner & Beane stated:

> The newer products, based on the company's unique fermentation process of sugar, molasses and corn sugar, include citric acid and derivatives, ascorbic acid, oxalic acid and oxalic acid salts, gluconic acid and gluconates. Riboflavin is also produced.

Pfizer was "believed to be the world's most important producer" of citric acid and "one of the largest producers of ascorbic acid (vitamin C)." [17]

In an analogous discussion of American Cyanamid, Merrill Lynch's survey said:

> American Cyanamid Co.'s aggressive administration of a long-term expansion program, has developed this company into a well-rounded organization which now ranks among the leaders in the chemical industry.
>
> * * * * * * *
>
> The five years 1928–33 were marked by aggressive acquisitions of smaller companies: Calco Chemical, one of the country's principal dyestuff producers, and 8 or 10 smaller units in the field; several companies producing textile chemicals; a plastics producer; a manufacturer of heavy industrial chemicals; Lederle Laboratories, an ethical drug house, and two small engineering companies. Since the middle 1930's, growth has been largely through research.[18]

Before contracts were signed with the OSRD under its penicillin synthesis program, Merck, Squibb, and Pfizer (though at first Merck and Squibb, without Pfizer) had been collaborating in research on penicillin—including both chemical structure and production techniques. "The Abbott, Lilly, Upjohn, and Parke, Davis laboratories collaborated in the midwestern area and with Dr. H. E. Carter of the University of Illinois as a consultant." [18a] According to a letter written by Reichel Laboratories on October 4, 1943, Reichel and Hoffman-LaRoche had entered into an agreement providing for a complete exchange between the two companies of information relating to penicillin.[19]

War Production Board Program for Further Expansion of Penicillin Production

In a memorandum which Dr. Elder referred to as having been written "some weeks" before a memorandum of February 24, 1944, which it accompanied, one of the topics was "Expansion of Existing Plants: In Suggested Order in Which They Should Be Approved." Among the various sorts of expansion discussed were the following: filling "up the existing building with tanks and extraction equipment," substituting "tanks for bottles," and making greater use of facilities already in place. In this connection, the proposal for four companies was: "Tanks to operate extraction equipment 24 hours per day and possibly more." [20]

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[16] Merrill Lynch, Pierce, Fenner & Beane, Chemical Industry Survey, 1943 edition, p. 30.

[17] Ibid., p. 48.

[18] Ibid., p. 24.

[18a] The Chemistry of Penicillin, p. 53.

[19] Reichel Laboratories, Inc., by John Reichel, to A. N. Richards, October 27, 1943, records of the OSRD, NA, RG 227.

[20] Undated copy of memorandum accompanying memorandum dated February 24, 1944, Dr. D. P. Morgan from Albert L. Elder, records of WPB, NA, RG 179.

The WPB Undertakes To Promote Interchange of Information and Encounters Patent Problems

On January 19, 1944, Dr. Albert L. Elder, head chemical adviser, Chemicals Bureau, WPB, and coordinator of its penicillin program, addressed to Fred J. Stock, Drugs and Cosmetics Section, WPB, a memorandum on the subject, "Exchange of Technical Data in the Penicillin Industry," in which the following passages appeared:

> * * * The simplest method for expanding the penicillin program today is that of increasing the efficiency of each plant now completed or in the process of completion. We should be criticized, and justly so, if every effort is not expended to obtain the maximum production possible out of these plants.
>
> As I look back on the program during the past few months during which I have attempted to coordinate this program, I realize that a grave mistake was made by me in accepting the responsibility of coordinating this program without at the same time having authority to increase the efficiency of a plant which had been approved prior to my participation in the program. As it was rather aptly put at the Industry Advisory meeting, I was not to be a bee going from one flower to another distributing pollen, but to be a collector of information. The data assembled thus far are now sufficient to convince me that we must have an exchange of information among all of the approved producers of penicillin if we are to save the lives of thousands of soldiers who will in all probability be casualties of war within the next few weeks. The value of penicillin in saving the lives of wounded soldiers has been so thoroughly demonstrated that I cannot with a clear conscience assume the responsibility for coordinating this program any longer while at the same time being handicapped by being unable to make available information which would result in the output of more penicillin and thereby save the lives of our soldiers.
>
> According to the agreement which you have made with the producers of penicillin it is my understanding that when in your opinion information was available which should be disseminated you would go before the companies and ask them to work out immediately suitable arrangements for the equitable distribution of such information. I appreciate that you must rely on my judgment as to whether or not such information now exists. It is my judgment that production of penicillin can be increased by the dissemination of such information. Therefore, I recommend that you take such steps as are necessary to see that technical information which can be of value and which is needed to further the production of penicillin be made available to the approved producers of penicillin.
>
> I believe that it is advisable for you to write a letter to each approved producer of penicillin and determine at once what arrangements they are willing to make for the complete exchange of technical information on the production of penicillin by fermentation methods.[21]

When the Penicillin Producers Industry Advisory Committee met on February 18, 1944, the purpose of the meeting was "to discuss penicillin production and requirements, to consider the desirability of pooling production information and experience, and to hear reports on the technical committee meeting in January and the status of research projects of OPRD and OSRD."[22] The rather detailed summary of the meeting prepared in WPB gives the impression that, before the

[21] Albert L. Elder to Fred. J. Stock, January 19, 1944, records of WPB, NA, RG 179.

[22] Summary, meeting of Penicillin Producers Industry Advisory Committee, February 18, 1944, p. 3, records of WPB, NA, RG 179.

subject of "pooling production information and experience" was reached on the agenda, discussion of a variety of problems had implicitly recognized the desirability of general interchange of information. The summary reported that—

> Dr. A. N. Richards, Chairman of OSRD's Committee on Medical Research, read a statement concerning OSRD activities in the field of chemistry and synthesis of pencillin. It included an account of the considerations which have guided and will continue to guide the Director of OSRD in the selection of companies with which contracts are made. A general description was given of the provisions of the contracts respecting disposition of patents and licenses and the principles to which the Director of OSRD would adhere in administering his responsibilities under the contract. An indication was given of the present state of knowledge of structure of penicillin, but no prediction can be made concerning the imminence of successful synthesis.[23]

While Dr. Richards' full statement has not been found, there was preserved in the OSRD files a document entitled "Penicillin Contract Patent Provisions," bearing a notation to the effect that it was written by John T. Conner (OSRD's General Counsel) and was read by Dr. Richards at the meeting of WPB's Industry Advisory Committee on February 18, 1944. As a relatively uncomplicated account of the provisions of OSRD's contracts with the commercial companies engaged in the penicillin synthesis program, as indicating rather clearly the attitude of OSRD, and as presenting to the Penicillin Industry Advisory Committee a definite plan for consideration, the statement is worthy of quotation in full:

Penicillin Contract Patent Provisions

> Very recently OSRD entered into several contracts calling for developmental work (classified as "Secret") on the synthesis of penicillin or a therapeutic equivalent. A few of the pharmaceutical firms had been carrying on for some time at their own expense research studies and investigations looking toward the synthesis of penicillin, and they and the other firms invited to participate in the program indicated a decided preference to finance the synthesis work from their own, rather than governmental, funds. Also, some of the pharmaceutical firms had already discovered valuable information, although mostly not of a patentable nature, and it was felt that it would be unfair to require them to assign to the Government titles to any patents issued thereafter and attributable to that information. OSRD's primary interest was to work out a procedure whereby the synthesis of penicillin for war casualty use could be expedited by a full interchange of information among all research teams working on the problem so that one team would not waste valuable time on work already done by another team.
>
> After giving the matter careful consideration, we finally worked out for use with the commercial organizations involved contract arrangements whereby (i) there is provided a complete interchange of information through OSRD of information discovered by all the OSRD contractors, (ii) the work being done by the commercial firms is financed by their own funds, and (iii) the OSRD is given the right to determine the disposition, among the organizations that make contributions through OSRD of valuable information or inventions, of all patents covering discoveries or inventions made under the contracts that are attributable to the interchange of information, through OSRD. In addition, the Government receives royalty-free licenses for mili-

[23] Summary, meeting of Penicillin Producers Industry Advisory Committee, February 18, 1944, p. 9, records of WPB, NA, RG 179.

> tary, naval, and national defense purposes under all patents resulting from work done by these OSRD contractors in the synthetic penicillin field, both before and after the execution of the OSRD contract. Also, OSRD has the right to require the OSRD contractors that ultimately become the titleholders of the patents to license other designated organizations, whether or not they are contributors of inventions or relevant information, upon the payment of reasonable royalties.
>
> Although under the contracts the OSRD receives rather broad powers in determining the disposition of patentable discoveries or inventions made in the course of the contract work that are attributable in whole or in part to information disclosed under the contracts to the participating organizations, Dr. V. Bush, OSRD Director, has pointed out that the contract provisions clearly indicate that it is not the intention of OSRD to have title to such patents vested in the Government in order to enable the Government to go into the business of manufacturing penicillin. In our opinion such a procedure would not be in the public interest and would constitute inequitable treatment not only of the ultimately successful inventor or inventors, assuming the inventor to be a commercial organization financing its own work, but also would constitute inequitable treatment of those commercial organizations whose skill, efforts, and financing have already resulted in the discovery of important relevant information and will undoubtedly continue to have that result during the course of the contract work.
>
> Dr. Bush has announced that the general policy governing the disposition of the patent rights by OSRD is that the public interest will be best served in this matter by a disposition of patent rights that will make available to the public through regular commercial channels an adequate supply of high quality synthetic penicillin or a therapeutic equivalent at reasonable prices that will include reasonable profits for manufacturing and distributing the product, Dr. Bush intends to arrange for the licensing on reasonable terms of any patents subject to disposition under the contracts in a manner designed to protect the public interest and the equities of the inventor and the pioneer and other organizations, American and British, which have already made or in the future may make valuable scientific or technical contributions toward the goal of synthesis.[24]

Dr. Elder had been present at the meeting of February 18, 1944, but a few days later, in the course of a memorandum dealing with various matters relating to penicillin he wrote again—this time (on February 24, 1944) to Dr. D. P. Morgan, Director, Chemicals Bureau, WPB—about exchange of technical data among penicillin producers:

> * * * There are three reasons why I believe that some mechanism should be set up for the exchange of technical information in such a new field as that of the production of penicillin. It should be borne in mind that the development of penicillin was not something which was originally created by American industry but which was called to our attention by the British. The output of penicillin by the different producers in the United States varies greatly. An exchange of information should do much toward bringing the poorer producers into line. A second reason for an exchange of information is that it is entirely possible that some one producer may make such a drastic improvement in the process that the total needs for penicillin could be met very quickly by applying this information to all of the production facilities.

[24] "Penicillin Contract Patent Provisions," read at meeting of Penicillin Producers Industry Advisory Committee, February 18, 1944, records of WPB, NA, RG 227.

> The third reason is that the patent situation with respect to penicillin may become quite complicated, and a royalty agreement made at this time would probably save a great deal of confusion at a later date. There are many applications for patents on the production of penicillin filed in the Patent Office at the present time. These have been placed under secrecy order by the Office of Scientific Research and Development. I have recommended against placing some of them under secrecy order but the OSRD has ruled that all of them be secret for the time being.
>
> No mechanism has been set up by which the War Production Board is kept fully informed on synthesis of penicillin. If such information is not made available, it is entirely possible that a fermentation expansion program might be launched at the same time that OSRD is developing pilot plant work on the synthesis of penicillin. This will certainly be a confusing picture and can easily arise.[25]

This second memorandum anticipated only slightly the WPB's bringing together on March 14, 1944, "19 major penicillin manufacturers in the United States and two from Canada * * * to explore the possibility of an agreement with the Government for the exchange, with other or prospective manufacturers of penicillin, of information concerning methods of producing penicillin by fermentation. * * *"

The press release announcing the meeting quoted "WPB officials" and reported their views in several paragraphs:

> The meeting is being called "because of the importance to the nation, particularly the fighting forces, of securing as rapid an increase in the production of penicillin as is humanly possible," they said.
>
> Officials explained that plant visits and reports have made it clear that if all firms manufacturing penicillin could be brought up to the rate of the most efficient the problem of adequate supplies for war needs would be largely met.
>
> "We have reason to believe that an exchange of information, both by written reports and by personal visits, could do a great deal to increase production," an official of WPB's Chemicals Bureau explained. "Experience in somewhat similar circumstances with the production of synthetic rubber has demonstrated the value of such arrangements."
>
> Tuesday's meeting will open with a general discussion of the whole problem after which a task group, which has been named, will discuss with Government representatives the details of an agreement.
>
> The members both of the larger group and the task committee will serve in a purely advisory capacity, WPB officials asserted, the War Production Board reserving the right to prepare a form of agreement which may not accord with the advice received. However, any such agreement will be binding upon any firm in the industry only to the extent that the firm is willing to accept it, the officials added.
>
> In order to afford the industry all proper protection under the antitrust laws, signatures to the agreement will be sought only if it is possible, as is expected, to secure the issuance of a certificate under section 12 of the Smaller War Plants Act covering activities contemplated by the contract, they asserted.
>
> A number of possible bases of agreement have been outlined to the manufacturers, according to Chemicals Bureau officials. Others may be suggested. In any case, it was said, it will be necessary to assume a require-

[25] Albert L. Elder to D. P. Morgan, February 24, 1944, records of WPB, NA 179.

> ment that any arrangement must be open to adherence of additional firms, merely upon their agreement to be bound by the provisions of the contract.
>
> The manufacturers also have been asked to consider in connection with each alternative, the possibility of a special provision that all purchases by the Government for its war requirements shall be free of the payment of royalties, the officials said.[26]

Of five possible bases of agreement that had been outlined to the manufacturers, one was described as analogous to "the synthetic penicillin contract," another as a "modification" of it.[27]

In the following press release issued on March 16, 1944, the WPB reported the meeting:

> With a view to increasing penicillin production, representatives of 21 producers have authorized a committee from their industry to explore, with the War Production Board, various forms of agreement for the exchange of technical information and patents, WPB announced today.
>
> The committee is to study possible contract forms and recommend an agreement between producers and WPB, which, it is hoped, may be concluded early next month.
>
> In granting authority for the explorations of the committee, producers' representatives expressed themselves as desirous of doing everything possible to increase the production of penicillin within the shortest period of time.
>
> The committee members are: A. H. Fiske, Eli Lilly & Co., Indianapolis, Ind.; H. C. Fritsch, Parke, Davis & Co., Detroit, Mich.; Carleton H. Palmer, E. R. Squibb & Sons, New York, N. Y.; Dr. John Reichel, Reichel Laboratories, Inc., Kimberton, Pa.; and Kenneth H. Hoover, Commercial Solvents Corp., Terre Haute, Ind.[28]

The circumstances attending the apparently extended explorations of the committee need not be related; but on June 5, 1944, D. P. Morgan, Director, Chemicals Bureau, WPB, and Harvey N. Davis, Director, Office of Production Research and Development, WPB, jointly addressed to Donald M. Nelson, Chairman, War Production Board, a memorandum which said (in part):

> It has been requested by the Penicillin Producers' Industry Advisory Committee * * * that arrangements be made whereby manufacturers of penicillin by fermentation processes may freely and voluntarily exchange technical information regarding such manufacture and various processes and materials used therein, with each other and with governmental representatives.
>
> * * * * * * *
>
> It is proposed that the Chairman of the War Production Board enable and request the penicillin producers listed to make available to one another technical information with respect to processes for the manufacture of penicillin by fermentation. * * *[28a]

A contract form accompanied the memorandum.

At a recent meeting of the Penicillin Producers Industry Advisory Committee, a representative of the Foreign Economic Administration had outlined substantially as follows the plans for distribution to other parts of the world:

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[26] WPB press release for March 13, 1944, records of WPB, NA, RG 179.

[27] Ibid.

[28] WPB press release for March 16, 1944, records of WPB, NA, RG 179.

[28a] D. P. Morgan and Harvey A. Davis to Donald M. Nelson, June 5, 1944, records of the WPB, NA, RG 179.

A control system for civilian distribution equivalent to that in the United States would be required of every foreign country to which shipments of penicillin were made, a FEA representative explained to the committee. Eighteen of the other American Republics thus far have notified FEA of their acceptance of this condition and have thus become eligible for penicillin allocations. FEA missions in the field have been instructed to determine that a penicillin committee is created in each country which has requested shipments. This committee would have the responsibility of approving all releases of penicillin within the country, and would be expected to adhere to the list of recommended medical uses of penicillin developed by Dr. Chester S. Keefer, of the National Research Council.

* * * sales would be made by American producers shipping to their agents on a commercial basis, but * * * the stocks held by these agents would be frozen and could be released only upon approval of the local penicillin committee. An attempt is being made by FEA to put this commercial sales plan into effect in all areas where commercial relations now exist. The allocation of one billion units was made largely as a move to acquaint doctors and hospitals in other parts of the world in its use.

Arrangements are now being made for the export of penicillin for restricted civilian use to European neutrals, the Middle East, the French areas, and other countries. It is expected that in the near future July quotas will be established for restricted civilian allocation of penicillin to India, New Zealand, Australia, South Africa, and the British West Indies, the FEA representative said.[29]

Encouraging as were the foregoing announcements, there was still no foreseeable limit to demand, and no reason to believe that greater production could not still be attained, if there were pooling of technical information. The obtaining of clearance from the Department of Justice permitting the exchange of technical information among penicillin producers, had first been discussed by the Penicillin Producers Industry Advisory Committee on February 18, 1944. A meeting of producers on March 14 and 15, 1944, had been devoted to consideration of this proposal. The immediate outcome had been the authorization of "a committee from their industry to explore, with the War Production Board, various forms of agreement for the exchange of technical information and patents"; and such a committee had been named.[30]

On June 21, 1944, Certificate 203 of the Chairman of the War Production Board to the Attorney General, approving the collaboration by manufacturers of penicillin "in the exchange of technical information respecting the production and processing of penicillin *derived by fermentation* [31] from *Pencillium notatum* and of any raw material or intermediate components of penicillin,[32] was duly signed. Accordingly, with the approval of the Penicillin Producers Advisory Committee, the WPB proceeded to call a 2-day technical meeting. This meeting, it was hoped could "take the form, substantially, of a round-table discussion" to consider "such technical phases of the manufacturing process as may be mutually helpful in the attainment and maintenance of a suitable penicillin production rate." In view of the present "urgent necessity of meeting high military requirements for penicillin," it was thought "appropriate" to bring together representatives of Government and industry "concerned with the technical phases" of penicillin production.

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[29] WPB press release, June 28, 1944, NA, RG 179.
[30] WPB press release, March 16, 1944, NA, RG 179.
[31] Italics supplied.
[32] 9 F. R. 7036 (June 24, 1944).

Continuing, the invitation to the meeting said:

> * * * There are a great many technical problems common to many or all of the producers of which no one organization has a perfect solution, but which may be advanced substantially toward solution by the putting together of the experience of a number of organizations, each of which knows a part of the requisite information. By this pooling of experiences, it is believed that rapid progress can be made toward the elimination of manufacturing difficulties and hence toward the rapid increase of the production rate of all concerned.
>
> Of the 25 companies expected to send representatives to the meeting, it is the writer's belief that each has information not held by any of the others that would be helpful to all, and that each is in a position to profit markedly from exchange of such information.
>
> The meeting planned will afford opportunity for the discussion of such recent results of research work in governmental laboratories as interests the producers.[33]

Despite its having been announced by the Chemicals Bureau of the War Production Board on March 28, 1944, that "no further major expansions" under the penicillin program would "be approved,"[34] the WPB apparently expected or hoped that new companies would undertake production. At any rate, it appears that not all of those invited to send representatives to the meeting were currently—and some of them may never have been—producers of penicillin.[35]

It is not known whether or not the meeting was considered to have been successful or whether other technical meetings were held. There is, however, a WPB internal report of a Penicillin Producers Industry Advisory Committee meeting on June 15, 1945, in which the following passage appears:

> Certificate No. 203, under section 12, Smaller War Plants Corporation, dated June 21, 1944, entitled "Manufacturers, Penicillin—Approval of Collaboration in Exchange of Technical Information."
>
> This certificate was approved some time ago in order to promote free interchange of technical information in order to bring about as large and efficient penicillin production as possible. The certificate protects the producers from any prosecution under the Antitrust Act. The question of revocation of this certificate was presented to the Committee and after some discussion it was recommended that the certificate remain in force.[36]

The OSRD Penicillin Synthesis Program

When Florey and Heatley came to America in 1941, the only method known for producing penicillin was by fermentation which, up to that date, had produced only small yields at extremely high cost. As early as 1931, however, Fleming had stated regarding penicillin: "It is quite likely that it, or a chemical of similar nature, will be used in the treatment of septic wounds." In commenting on this remark in 1944, Fleming stated:

> The words "chemical of a similar nature" were prompted by the thought that some day a chemist would discover the nature of the active principle, synethetize it, and use either that or some modification as a chemotherapeutic

[33] WPB letter, dated July 6, 1944, sent to 25 United States companies, NA, RG 179.
[34] WPB press release, March 28, 1944, NA, RG 179.
[35] FTC data request, 1957.
[36] Memorandum, J. Solon Mordell to George K. Hamill, June 20, 1945, records of WPB, NA, RG 179.

agent. That was years before the introduction of the sulphonamides and at a time when the only effective antibacterial chemotherapy was the treatment of syphilis by modifications of Ehrlich's salvarsan.[37]

Efforts during the intervening years to discover the nature of the active principle and synthesize it had been unsuccessful. If it could be done, however, the production of penicillin in volume by synthesis was still regarded as highly desirable. Therefore, although production by fermentation was the method fostered by the OSRD, research respecting the chemical structure of penicillin was also undertaken both by some of the producing companies and by non-producing research organizations. Prior to the middle of 1943, however, it appears that there were no concrete proposals for speeding synthesis and information respecting the results of such research was being shared only to a limited extent. "Two of the seven companies" then producing penicillin, said Richards, "are sharing information, viz: Merck and Squibb, I believe, by formal agreement. Pfizer, to some extent, shares with Merck and is contemplating sharing also with Squibb. Otherwise there is no pooling." The most important question related to synthesis was: "To whom and under what conditions is penicillin to be assigned for chemical study which may lead to synthesis?" [38]

About the middle of August 1943, OSRD took the first serious steps toward organizing and coordinating synthesis research. The following quotations are the highlights of a four-page summary of discussion had at a meeting of OSRD representatives on August 17, 1943: [39]

> The problem is to assure the largest possible production of this drug in the shortest time. This will necessitate adroit action to compensate for commitments and debts already made and the careful avoidance of any further commitments until an overall plan is at least in mind. * * *
>
> Once the structure of penicillin is elucidated, the synthesis should follow reasonably soon and as present indications point to a relatively simple molecule the synthetic product would be far cheaper than the natural. * * *
>
> * * * * * * *
>
> Promotion of work on the synthesis is an important matter. It was agreed that everything should be done to expedite it. * * *
>
> * * * * * * *

Soon after the first meeting of the WPB's Penicillin Producers' Industry Advisory Committee, Dr. Richards made what appears to have been the first direct approach to individual companies looking toward the organization of chemical research on penicillin under OSRD auspices. On October 2, 1943, he addressed the following letter to the nine companies then engaged in the manufacture of penicillin, the same letter, with appropriate changes, being sent also to eight more companies said to "have WPB sanction to undertake production" of penicillin.

> You are aware of a decision communicated by Mr. Stock of WPB to the members of the Penicillin Producers' Industry Advisory Committee at their meeting on September 22 to the effect that the Government interests in all questions concerning production of penicillin are henceforth to be

[37] Alexander Fleming, "The Discovery of Penicillin," British Medical Bulletin (vol. 2, 1944, No. 1, p. 5).
[38] A. N. Richards to Vannevar Bush, August 14, 1943, records of OSRD, NA, RG 227.
[39] R. L. Waterman to A. N. Richards and Carroll L. Wilson, August 19, 1943, records of OSRD, NA, RG 227.

cared for by WPB; whereas Government interest in scientific research in the fields of the clinical testing and the chemistry of penicillin is the responsibility of the Office of Scientific Research and Development.

As Chairman of the Committee on Medical Research, to which a share of the responsibility of OSRD has been delegated, I wish to place before you a statement of the problems which confront us and to invite the assistance of your comments and advice in their solution.

1. Investigations designed to lead to discovery of a method of synthesizing penicillin or its therapeutic equivalent are regarded as urgently important as an item in the war effort. Hence Government must undertake to expedite chemical investigations.

2. Nine commercial firms, of which yours is one, are now producing penicillin; eight others have WPB sanction to undertake production; still others, in limited number, may later be encouraged to participate in the production effort.

3. Some of the nine and some of the eight companies above referred to maintain chemical research staffs of various degrees of scientific investigative capacity.

4. In some companies the research staffs have made important progress in the direction of elucidation of the structure of penicillin; others have made good beginnings; still others are eager to contribute investigative knowledge but for one or other reason have not yet been able to make an effective beginning.

5. If a method for synthesis is discovered which is capable of development into production processes more economical than are the fermentation methods now in use, it may be assumed that most, if not all, of the companies now or soon to be engaged in production will desire to engage in synthetic production.

6. It is assumed that progress toward the goal of synthesis can be accelerated by pooling of information among all of those research groups who are or shall be devoting themselves to this study.

7. The present supply of penicillin is far from adequate to meet the needs of the Armed Forces, to say nothing concerning legitimate civilian needs. Chemical research which uses penicillin is therefore made at the cost of lives as well as of dollars. This cost is justified by confidence in the belief that the achievement of an earlier abundance of the drug will far more than compensate for the present necessary restrictions. This justification is true, however, only if allocation for chemical research is restricted to those chemists whose capacities are best suited to successful attack upon the problem of synthesis.

8. What principle should govern the selection of commercial companies to which penicillin should be allocated for chemical research, the aim being to obtain the greatest yield of information from a limited amount of material?

9. Upon what terms can full interchange of chemical research information be arranged among the research groups of the commercial companies whose accomplishments differ in degree; at the same time doing justice to those whose initiative, energy, and skill have already advanced the problem to a stage at which the prospect of achievement of synthesis is promising?

In the interchange of information above referred to it may be understood that the Department of Agriculture's laboratory at Peoria will par-

ticipate, as will also such university laboratories as may be enlisted, under contract with OSRD, to undertake chemical research on penicillin.

It was announced at the meeting on September 22 that a committee, advisory to the Committee on Medical Research in all matters connected with chemical research in penicillin, including policy governing allocation for chemical research, would be appointed. That committee has now been formed and consists of Hans T. Clarke, chairman; Roger Adams, R. D. Coghill, and William Mansfield Clark.

This letter is being sent to the head of each of the companies which were represented at the meeting on September 22. It does not imply a commitment by OSRD with respect to allocation of penicillin to your firm for chemical research; nor will your reply, which will be treated as confidential, be regarded as committing your firm in any contractual sense to opinions or recommendations expressed in it. You are urgently requested to give your immediate attention to the problems stated in it and to reply as promptly as possible. It would be most helpful if, as a crystallization of your comments and advice, you would outline an agreement which you might be willing to undertake with the Government and which you believe would enable the OSRD to fulfill its obligations to this military problem.[40]

The responses to Richards' letter were various. Some companies thought that they were and would probably continue to be fully occupied with production problems; others in effect disclaimed competence for the task; still others were noncommital or vague. Most of those who intimated that they might participate seemed to be principally concerned about patent problems.

A special committee was appointed to select firms to engage in research on the synthesis of penicillin. This committee reported on November 19, 1943, naming 10 companies which it recommended "be invited to enter into contractual relations with regard to the exchange of information concerning the chemistry of penicillin." The committee also listed six other companies which either had expressed lack of interest in the projected synthetic investigations, or were regarded by the committee as not meeting the qualifications set up. The committee also recommended that certain noncommercial and academic chemists be invited to participate in the project.[41]

Contract forms covering the proposed cooperation were drawn up and submitted to the companies. In the letter enclosing the proposed contract, Dr. Bush wrote in part:

In arriving at your decision, I think that it will be helpful for you to have before you several considerations in addition to those discussed in Dr. Richards' October 2nd letter. In the first place, we have every reason to believe that OSRD will soon be in a position to reveal to those organizations accepting the provisions of the enclosed contract form some important information recently discovered in England, which, together with information already in your possession, may quickly lead to a solution of the problems of synthesis. Also, OSRD will probably be the channel through which information hereafter discovered in England concerning synthesis is to be transmitted to organizations in this country. [An attempt would be made, it was said, to work out reciprocal arrangements with the British Government.] * * *

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[40] A. N. Richards to "nine firms * * * producing penicillin" and to "eight firms to undertake production," October 2, 1943, records of OSRD, NA, RG 227.

[41] H. T. Clarke, chairman, Roger Adams, and R. D. Coghill, November 19, 1943, to Director of OSRD, records of the OSRD, NA, RG 227.

> Secondly, although Article 3 (b) of the enclosed form gives the OSRD contracting officer rather broad powers in determining the disposition of patentable discoveries or inventions made in the course of the subject work which are attributable in whole or in part to information disclosed under the contract to the Contractor, the contract provisions show that it is not our intention to have title to such patents vested in the Government in order to enable the Government to go into the business of manufacturing penicillin. In my opinion such a procedure would not be in the public interest and would constitute inequitable treatment not only of the ultimately successful inventor or inventors but also of those organizations whose skill, efforts and financing have already resulted in the discovery of important relevant information and will undoubtedly continue to have that result during the course of the subject work under the contracts.
>
> The procedure that I have in mind contemplates the selection of a small, impartial, disinterested committee of outstanding men which I shall call upon for advice and recommendations on problems arising under the contracts concerning the disposition of patent rights that call for a decision by the OSRD Contracting Officer. The general policy that I intend shall govern the advisory recommendations of that committee and my decisions is that the public interest will be best served by a disposition of patent rights that will make available to the public through regular commercial channels an adequate supply of high quality synthetic penicillin or a therapeutic equivalent at reasonable prices which will include reasonable profits for manufacturing and distributing the product. It is my intention to arrange for the licensing on reasonable terms of any patents subject to disposition under Article 3 in a manner designed to protect the public interest and the equities of the inventor and the pioneer and other organizations, American and British, which have already made or in the future may make valuable scientific or technical contributions toward the goal of synthesis. For example, the group of collaborating American firms composed of Squibb, Merck, and Pfizer is contributing what is believed to be the chemical structure of penicillin. If synthesis proves their structure to be substantially correct, the value of their contribution will probably be such that, in making an equitable distribution of patent rights governed by Article 3 (b) of the OSRD contracts, I intend to grant such firms at least royalty-free licenses under United States patents, even if the synthesis invention is made by an OSRD contractor not a member of that group.
>
> Your firm has already indicated that it is willing to license organizations designated by the Government under your patents, and that understanding is reflected in the provisions of Article 3. In view of the fact that the Government itself has made some scientific contributions and has already financed and will probably continue to finance clinical experiments building up a market for penicillin, we feel that it only equitable for the Government to receive a royalty-free license under patents governed by Article 3.[42]

In the volume, Organizing Scientific Research for War, "one of a series devoted to the history of the Office of Scientific Research and Development," [43]

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[42] Vannevar Bush to prospective commercial participants, various dates in December 1943, NA, RG 227. The quoted paragraphs appeared in all transmittal letters accompanying contracts. Letters to prospective contractors other than Merck, Squibb, and Pfizer, however, contained a paragraph saying in effect that if the theory that "Government financing [was] neither desired nor necessary" should be incorrect, appropriate changes in the contract could be made.

[43] Irvin Stewart, Organizing Scientific Research for War, The Administrative History of the Office of Scientific Research and Development, Little, Brown & Co., Boston, Mass., 1948, p. xi.

Irvin Stewart devotes a chapter to "Patent Policy," much of which is concerned with discussion of the formulation and use of the patent clauses in OSRD contracts—"long form" and "short form." Of these it was said: "OSRD adhered closely to the two standard forms of patent clause as being adequate to meet all situations. * * * Believing that uniformity of language was essential if the possibilities of later misconstruction of intent were to be minimized, OSRD permitted few variations from the standard clause," and these "were largely by way of additions to the standard clause." [44]

To the views expressed and the practices described, the OSRD did not, however, adhere with rigid consistency, as Stewart indicates in the following paragraph, which affords a useful summary of the major provisions of the patent clause of the penicillin synthesis contracts and states the reasons for the special features of that clause:

> An entirely different patent clause was used in a group of contracts directed toward the synthesis of penicillin or a therapeutic equivalent thereof. The commercial organizations most concerned had been carrying on research in the field at their own expense for some time and they desired to continue at their own expense. Some of them had already discovered valuable information although mostly not of a patentable nature. OSRD's primary interest was to work out a procedure whereby the synthesis of penicillin for war casualty use could be expedited by a full interchange of information among all research teams so that one team would not waste valuable time on work already done by another team. With the advice of the Commissioner of Patents and after clearance with the Department of Justice, an arrangement was worked out with the commercial organizations under which (1) there would be complete interchange through OSRD of information discovered by all the OSRD contractors; (2) the commercial organizations would continue to finance their own work, and (3) OSRD would have the right to determine the disposition, among the organizations that made contributions through OSRD of valuable information or inventions, of all patents covering discoveries or inventions made under the contracts that were attributable to the interchange of information through OSRD. In addition the Government was to receive a royalty-free license for military, naval, and national defense purposes under all patents resulting from work done by these contractors in the synthetic penicillin field, both before and after the execution of the OSRD contracts. Finally, OSRD was given the right to require contractors who would ultimately become the titleholders of the patents to license other designated organizations, whether or not they contributed inventions or relevant information, upon payment of reasonable royalties.[45]

There seems never to have been much doubt on the part of OSRD that immunity from the antitrust laws could be obtained to protect participants in the synthesis program in the exchange of information developed under their contracts. But it was not until December 7, 1943, that the desired clearance was obtained.[46] After some delay a total of nine contracts were signed with what were called "the American Commercial Participants" and the Government of the United States as represented by the Director of the Office of Scientific Research and Development. The list of contracting companies, and the periods covered by the contracts is as follows:

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[44] Op. cit., p. 225.

[45] Ibid, pp. 225–226.

[46] Certificate No. 187, "Proposal for Collaboration between Certain Companies and the Government" was signed by Donald M. Nelson, Chairman, War Production Board, on December 7, 1943—8 FR 16,772 (December 14, 1943).

Abbott Laboratories, North Chicago, Ill., OEMcmr–396, from December 15, 1943, to October 31, 1945.

Eli Lilly & Co., Indianapolis, Ind., OEMcmr–397, from December 15, 1943, to October 31, 1945.

Merck & Co., Inc., Rahway, N. J., OEMcmr–391, from December 1, 1943, to October 31, 1945.

Parke, Davis & Co., Detroit, Mich., OEMcmr–398, from December 15, 1943, to October 31, 1945.

Chas. Pfizer & Co., Inc., New York, N. Y., OEMcmr–390, from December 1, 1943, to October 31, 1945.

Shell Development Company, San Francisco, Calif., jointly with Cutter Laboratories, Berkeley, Calif., OEMcmr–445, from April 15, 1944, to October 31, 1945.

E. R. Squibb & Sons, New York, N. Y., OEMcmr–389, from December 1, 1943, to October 31, 1945.

The Upjohn Co., Kalamazoo, Mich., OEMcmr–399, from December 15, 1943. to October 31, 1945.

Winthrop Chemical Co., Inc., New York, N. Y., jointly with Heyden Chemical Corp., Garfield, N. J., OEMcmr–428, from December 15, 1943, to October 31, 1945.[47]

In addition, contracts and letter agreements were made with what were known as "the American Non-Commercial Participants." These contracts provided "for related studies and experimental investigations" during the periods covered, which were of varying duration. The American Non-Commercial Participants, with the numbers and dates of their contracts or letter agreements, were:

U. S. Department of Agriculture, Bureau of Agricultural and Industrial Chemistry, Northern Regional Research Laboratory, OEMcmr–410, from December 1, 1943, to October 31, 1945.

Cornell University OEMcmr–411, from January 1, 1944, to December 31, 1945, and OEMcmr–542, from April 1, 1945, to December 31, 1945.

Federal Security Agency, Food and Drug Administration, OEMcmr–465, from June 1, 1944, to October 31, 1945.

Harvard University, OEMcmr–540, from May 1, 1945, to December 31, 1945.

University of Illinois, OEMcmr–439, from April 15, 1944, to December 31, 1945.

University of Michigan, OEMcmr–408, from January 1, 1944, to December 31, 1945, and OEMcmr–442, from April 15, 1944, to December 31, 1945.

Department of Commerce, National Bureau of Standards, from March 17, 1945, to December 31, 1945.

U. S. Naval Medical Research Institute, from May 7, 1945, to December 31, 1945.

Rockefeller Institute for Medical Research, from April 13, 1945, to December 31, 1945.

Stanford University, OEMcmr–561, from June 1, 1945, to December 31, 1945.

B. E. Warren, MIT, from April 13, 1945, to December 31, 1945.

Dean F. C. Whitmore, Penn State, from December 30, 1944, to December 31, 1945.

Milton Veldee, U. S. Public Health, from October 7, 1944, to December 31, 1945.[48]

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[47] Interim first determinations of the Director of OSRD under the penicillin synthesis contracts, April 15, 1946, records of OSRD, NA, RG 227.

[48] Interim first determinations of the Director of OSRD under the penicillin synthesis contracts, April 15, 1946, records of OSRD, NA, RG 227.

Prior to the initiation of this collaborative penicillin synthesis program as organized in December 1943, under OSRD auspices, "considerable progress had been made on the isolation and structure of penicillin in several laboratories. Some of this research was also collaborative." Concerning that research the official report on the program said:

> In the eastern area, the Merck and Squibb laboratories collaborated and were later joined by Pfizer. These three laboratories also exchanged progress reports with certain cooperating laboratories in Great Britain, including those constituting the Therapeutic Research Corp. When the secrecy order was issued, reports were exchanged through the Committee of Medical Research of the Office of Scientific Research and Development.
>
> The Northern Regional Research Laboratory also reported the results of investigations upon the production and chemistry of penicillin.
>
> The Abbott, Lilly, Upjohn, and Parke, Davis laboratories collaborated in the midwestern area, and with Dr. H. E. Carter of the University of Illinois as consultant. (The Chemistry of Penicillin, p. 53.)

During the period that the OSRD contracts were in effect, marked improvement in the technology of penicillin production and the development of more productive strains of the mold greatly increased production attainable by fermentation. In May 1945, Dr. Roger Adams (one of the members of the committee that had selected the American commercial participants in the OSRD penicillin synthesis program) had said in a letter to OSRD's General Counsel, Oscar M. Ruebhausen:

> * * * The low absolute cost of fermentation penicillin is such that the achievement of synthetic penicillin becomes more academic and of less significance from the standpoint of the nation. I see no reason why synthetic penicillin would be of greater medical usefulness. * * * [49]

And on August 24, 1945, it was announced that, effective August 31, all WPB restrictions on the "use and allocations" of penicillin would be removed.[50] By this time there was little worry about the continued production of adequate supplies of penicillin by fermentation.

After the expiration of the contracts, "investigation continued by the Cornell group as an independent project, led to the isolation early in 1946 of synthetic benzylpencillin in crystalline form." [51] By this time, however, the accomplishment of synthesis had become truly academic, for it was never put to practical use in penicillin production for the reason that penicillin could be produced at less cost by fermentation.

The United States Department of Agriculture in the History of Penicillin

On March 4, 1946, the Agricultural Research Administration of the United States Department of Agriculture issued a "Research Achievement Sheet." The heading of its single page of text was: "Penicillin Made Available Through Agricultural Research"; and its most significant paragraph was the following:

> Within a year after Dr. Florey took his problem to the Northern Laboratory, important discoveries and developments had made commercial produc-

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[49] Roger Adams to Oscar M. Ruebhausen, May 18, 1945, records of OSRD, NA, RG 227.

[50] WPB press release, August 24, 1945, records of WPB, NA, RG 179.

[51] "The Chemistry of Penicillin," p. 9, n. 9. Ibid., Vincent du Vigneaud, Frederick H. Carpenter, Robert W. Holley, Arthur H. Livermore, and Julian R. Rachele, "Synthetic Benzylpenicillin," and the same authors' paper, "Synthetic Penicillin," Science, vol. 104 (Nov. 8, 1946), pp. 431–433, 450.

> tion of penicillin feasible. One of the first discoveries of the laboratory scientists was that yields of penicillin could be greatly increased by adding corn-steep liquor (a byproduct of cornstarch manufacture) and lactose (milk sugar) to the culture medium in which the mold is grown. In seeking higher yielding strains, molds from many parts of the world were brought to the laboratory for testing, but the highest yielder was found growing on a cantaloup in a Peoria market. Other accomplishments of the research workers were improved methods of recovery and purification of penicillin.

A year before this announcement was made, Dr. Charles Thom whose contributions to the penicillin program as an employee of the Department of Agriculture have previously been cited, concluded an account of how arrangements were made "to turn * * * over to the Northern Regional Research Laboratory" the problem which Florey and Heatley had brought to the United States for solution. "Thus," he wrote, "the penicillin project reached America and fell into the hands of a great government laboratory from which has come most of the fundamental work that has made large scale production possible." [52]

A more complete listing of the contributions of the Northern Laboratory was given some 2 years later in the "Summary" which concluded the chapter, "Research in the Development of Penicillin," by Kenneth B. Raper,[53] in Advances in Military Medicine, the two-volume official record of medical progress during the war edited by members of the Committee on Medical Research of the Office of Scientific Research and Development. This summary stated:

> Research on penicillin production at the Northern Regional Laboratory has been paralleled by investigations of a somewhat similar nature carried on in many other laboratories. Current production of this drug is, of course, based on the knowledge gathered in the sum of such studies. This laboratory, working with the Committee on Medical Research, however, takes justifiable pride in having supplied much of this essential information. Briefly summarized, the principal contributions of this laboratory may be listed as follows:
>
> (1) Development of the corn steep-lactose media for penicillin production.
>
> (2) Demonstration that penicillin could be produced in submerged culture.
>
> (3) Production of increased penicillin yields by the addition of phenylacetic acid.
>
> (4) Improvement and refinement of assay methods.
>
> (5) Isolation of new penicillin-producing molds and the development of superior strains capable of greatly increased production.
>
> (6) Distribution of proved cultures to industries and research laboratories investigating penicillin.
>
> (7) Definition of certain factors affecting the stability of penicillin.

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[52] Charles Thom, "Mycology Presents Penicillin," Mycologia, vol. 37, 1945, p. 467.

[53] Dr. Raper was himself a leading participant in penicillin research and, like Dr. Thom, a mycologist. (Cf. "The Fungi Come Into Their Own," Mycologia, vol. 44, 1952, p. 276, where E. O. Dodge refers to Thom and Raper's "60 man-years of culture work on the Penicillia," and states further that: "* * * when there came calls in 1941 for cultures of strains of *Penicillium notatum* for studies on the production of the antibiotic penicillin, Thom and Raper were ready to supply not only cultures of 30 or 40 strains of *Penicillium notatum* and a hundred or so strains of *P. chrysogenum*, but also 2,000 cultures of other species of *Penicillium*. This number was eventually increased to about 4,000. Until 1941 you could not have found over a dozen *Penicillium* specialists even if you searched laboratories all over the world. But very soon there were hundreds, maybe thousands, of workers, if you include bacteriologists, chemists, pharmacologists and engineers, in addition to mycologists, who turned their attention to the Penicillia and other fungi.")

(8) Development of a carbon process for penicillin recovery.
(9) Preparation of crystalline benzylamine derivatives of the penicillins.
(10) Isolation and characterization of penicillin X.
(11) Preparation of the azopenicillins and other derivatives.
(12) Preparation and characterization of the International Penicillin Standard.[54]

The achievements listed above were never considered to be of equal importance, and high hopes entertained for some discoveries have not been realized. Penicillin X, isolated at the Northern Regional Research Laboratory, was perhaps the outstanding disappointment, regarding which it was subsequently reported:

> * * * Penicillin X was at first thought to offer possibilities as a drug entity, because it was shown to be more effective than penicillin G against streptococci, pneumococci, and gonococci. Differences in effectiveness between penicillins X and G, however, were soon found to be quantitative rather than qualitative and did not warrant the manufacture of penicillin X with its much higher production costs.[55]

Some of the achievements require for their explanation more technical discussion than is here appropriate. Others need only be stated for their importance to be recognized. Among the latter is the fact that the laboratory supplied the initial stimulus to the work on adjuvants or precursors, which later was fruitfully developed by other investigators. Regarding this it has been said:

> A development of great technical importance resulted from the observation, first recorded by the Northern Regional Research Laboratory (Report to the Committee on Medical Research, No. 16) that the addition of phenylacetic acid and related compounds to media in which penicillin is elaborated in surface culture gives rise to increased yields of antibiotic products. Attempts to induce a similar effect with submerged cultures having failed, the chemists of the Lilly Research Laboratories, in an extensive survey, discovered (*L. 12*) that the yields of penicillin could be raised by the addition of phenylacetyl derivatives of various L-amino acids. * * *[56]

Another field in which the Peoria Laboratory made an important contribution was the development of improved cultures for use in submerged fermentation. Regarding this, Raper has stated that: "As it became apparent that the submerged fermentation was industrially feasible, the need for developing higher yielding submerged cultures was recognized." There was accordingly instituted the tremendously successful program described in detail below:

> Strain NRRL 832, the culture employed for this type of production, was studied intensively. Efforts to obtain from it a natural variant characterized by substantially increased production were unsuccessful. Attention was then directed toward the isolation of new strains from nature. Previous work had shown that almost all members of the *P. notatum-chrysogenum* group produced some penicillin. It seemed probable, therefore, that new strains possessing greater productive capacity than NRRL 832 might be obtained if a larger number of isolates were examined. Such a search was undertaken early in 1943.

[54] Advances in Military Medicine, edited by E. C. Andrus et al., 2 vols., Little, Brown & Co., Boston, 1948, vol. 2, p. 745.
[55] Yearbook of Agriculture 1950–51, p. 736.
[56] The Chemistry of Penicillin, p. 9.

> New cultures were obtained from moldy food products, fruits and vegetables in early stages of spoilage, and from fertile soil collected from various stations in the United States and from many foreign countries.[57]

The "Air Transport Command assisted * * * materially in securing" molds from widely separated areas and may have helped to set a precedent followed in organizing many of the searches for new antibiotic agents undertaken in succeeding years. Raper has stated that "in the handling of these cultures, a simple screening test was developed, which effectively weeded out the less productive strains, while the more promising ones were studied thoroughly in surface, and in shaken-flask, cultures."[58] Regarding the results of this work on cultures at Peoria, it has been stated:

> The most important culture discovered, however, was isolated from a moldy cantaloupe in Peoria. The culture represented a strain of *Penicillium chrysogenum* Thom, a species closely allied to *P. notatum*, and was designated "NRRL 1951" in our collection of cultures. When first studied, it produced penicillin in slightly greater yields than NRRL 832, but within a few months a natural variant, which more than doubled the amount, was developed from it. This substrain, designated "NRRL 1951.B25," was studied intensively here, and was at the same time made available to the penicillin industry in 1944. It was soon generally adopted for submerged production.[59]

Another example of the fruitfulness of work begun at Peoria has been described as follows:

> Early in 1944, faced with the demand for ever-increasing amounts of penicillin, and fully cognizant of the progress that had been made in the development of more productive cultures at this laboratory, the Office of Production Research and Development of the War Production Board set up projects at various institutions to explore vigorously each of the several approaches to the problem of obtaining additional cultures characterized by increased penicillin production.[60]

Raper has described the basis for, and the results of thus expanding the work already done at the Northern Regional Research Laboratory as follows:

> * * * it then seemed probable that cultures capable of producing greatly increased yields of penicillin might be obtained by one or more of the following means: The isolation of new strains from nature; the selection of natural variants from such new stocks; and the production of induced mutations from known good producing strains by X-ray and ultraviolet radiation, or by other artificial means.
>
> At the Carnegie Institution a mutation was produced that possessed outstanding merit. This culture, designated "X–1612," was produced by X-ray radiation of spores of NRRL 1951.B25. It was first tested at the University of Minnesota, but its real potentialities were established at the University of Wisconsin in small vat fermenters. The superiority of the strain was subsequently verified at this laboratory. Yields more than twice those produced by NRRL 1951.B25 were obtained from X–1612 and it soon

[57] Kenneth B. Raper, "Penicillin," Yearbook of Agriculture, 1943–47, pp. 702–703.

[58] Kenneth B. Raper, "The Development of Improved Penicillin-Producing Molds," Annals of the New York Academy of Sciences, vol. XLVIII, art. 2, Sept. 27, 1946, p. 42.

cultures at Peoria, it has been stated:

[59] Kenneth B. Raper, "Penicillin," Yearbook of Agriculture, 1943–1947, p. 703.

[60] Advances in Military Medicine, edited by E. C. Andrus et al., 2 vols., Little, Brown & Co., Boston, 1948, vol. 2, p. 737.

supplanted the parent culture as the principal strain for commercial production.[61] Another great step forward was made by exposing spores of X–1612 to ultraviolet. In this way, the Wisconsin group succeeded in producing a mutation, designated "Q–176," which doubled the yield produced by strain X–1612. The development of this outstanding culture for submerged production can be summarized as follows:

NRRL 1951	P. chrysogenum, isolated from a moldy cantaloupe, capable of producing approximately 100 u/ml. of penicillin in submerged culture.
NRRL 1951.B25	A naturally occurring variant from NRRL 1951, capable of producing up to 250 u/ml. of penicillin.
X–1612	An X-ray induced mutation from NRRL 1951.B25, capable of producing more than 500 u/ml. of penicillin.
Wis. Q–176	An ultraviolet-induced mutation from X–1612, capable of producing more than 900 u/ml. of penicillin.

The importance of the foregoing developments to present penicillin production cannot be overemphasized, because current yields of 750 to 900 units per milliliter are obtained in nutrient solutions of approximately the same composition as those used to produce maximum yields of 75 to 100 units per milliliter with NRRL 832 just a short time ago.

Some difficulties were encountered when these high-yielding strains were first adopted for commercial production, for they were found to produce primarily penicillin K, a type that is rapidly destroyed in the animal body and hence is much less useful clinically. However, if phenylacetic acid or phenylacetamide is added to the production medium, these strains can be made to produce primarily the more useful penicillin G. This procedure has been adopted by industry.[62]

Only a few years later it was possible to write: "* * * The cumulative result of all the studies [of penicillin cultures] was the development of a culture capable of yielding 900 to 1,000 units per milliliter of penicillin, in contrast to 75 to 100 units per milliliter obtainable from the unimproved

---

[61] Raper has stated further: "The production of this culture should be regarded as a joint endeavor. The stock was supplied by the Fermentation Division, Northern Regional Research Laboratory; the irradiation was performed by Dr. Demerec and associates at Cold Spring Harbor; the initial and indicative production tests were made at the University of Minnesota, by Drs. Christensen and Ehrlich; and the real magnitude of its superiority was demonstrated, at the University of Wisconsin, by Professors Peterson and Johnson in 80-gallon fermenters." (Kenneth B. Raper, "The Development of Improved Penicillin-Producing Molds," Annals of the New York Academy of Sciences, vol. XLVIII, art. 2, Sept. 27, 1946, p. 45.)

Also, writing of X–1612 in its report for the fiscal year ended June 30, 1945, the Bureau of Agriculture and Industrial Chemistry of the United States Department of Agriculture commented: "This organism, known as X–1612, has produced 450 units of penicillin per milliliter in experiments at the Northern Regional Laboratory. If the recovery problem or some other difficulty does not interfere with the general industrial adoption of X–1612, a further marked increase will occur in penicillin production without any increase in manufacturing facilities. The tremendous value of a better mold strain cannot be overemphasized. With apparent penicillin production in 1945 of approximately 8,500 billion units, which will sell for about 60 million dollars, an organism that can increase production by only 10 percent without additional cost would be worth 6 million dollars a year." (Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Dept. of Agriculture, Report for the Fiscal Year ended June 30, 1945, p. 21.)

[62] Kenneth B. Raper, "Penicillin," Yearbook of Agriculture, 1943–47, pp. 703–704.

> parent. This culture is still universally employed for the manufacture of penicillin in this country and abroad, and additional selections and mutations have undoubtedly been developed in the research laboratories of the pencillin industry to increase productivity further.[63]

Another highly important contribution of the Peoria laboratory to the technology of penicillin production was "submerged, or tank, culture." Regarding this, Kenneth B. Raper and Robert G. Benedict wrote in the Yearbook of Agriculture, 1950–51:

> From an economic standpoint, this method was particularly attractive and soon supplanted all other methods of manufacture. It reduced labor costs and increased productive capacity enormously. At the same time it obviated the need for large and expensive incubators and the special machinery required to handle the tremendous number of bottles or other containers formerly used in producing penicillin by surface-culture techniques.[64]

Testimony to the same effect comes from Pratt and Dufrenoy, who say:

> Substitution, in 1944, of "submerged culture" technics for the original "surface culture" methods made possible much more efficient operating methods. From statistical data available from a penicillin plant [Data from the Cutter Laboratories, Berkeley, Calif.], it may be estimated that conversion from "surface" to "submerged" fermentation increased the amount of penicillin produced 20-fold in terms of space required for biosynthesis, and 72-fold in terms of man hours.[65]

Of particular interest in this connection is the judgment of the British scientist, A. L. Bacharach,[66] of Glaxo Laboratories, Ltd. This British authority has stated:

> It is pertinent to ask why what has happened has in fact happened. How has it been possible to step up manufacture, taking the two countries [the United Kingdom and the United States] together, from nothing to over 300 tons in 10 years and how has it been possible to replace a relatively crude hygroscopic freeze-dried material, containing not more than 20 percent or 30 percent of the active antibiotic, by a white crystalline substance, conforming with pretty rigid pharmacopoeial standards, of over 95 percent purity? The answer can be given shortly, if somewhat cryptically, in the single word "*titers.*"[67] This is the fermentation technologist's jargon for the content of his final product per unit of fermentation liquid. The higher this is, the greater are the economies in production, and for two distinct reasons. First of all, more active product is being produced per unit of raw material and per unit of capital invested in the plant; and, secondly, the process of purification becomes proportionately easier as the amount of "muck" (including water) to be removed is reduced.

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[63] Kenneth B. Raper and Robert G. Benedict, "Drugs of Microbial Origin," Yearbook of Agriculture, 1950–51, p. 735. As of 1952, Raper believed penicillin yields exceeding 1,500 units per milliliter to be "not uncommon." (Kenneth B. Raper, "A Decade of Antibiotics in America," Mycologia, vol. 44, 1952, No. 1, p. 13.)

[64] Op. cit., "The Drugs of Microbial Origin," p. 735.

[65] Robertson Pratt and Jean Dufrenoy, Antibiotics, 2d ed., J. B. Lippincott Co., Philadelphia, 1953, pp. 56–67.

[66] Coauthor, with B. A. Hems, of the chapter, "Chemistry and Manufacture of Penicillin," in the volume of which Sir Alexander Fleming was general editor, Penicillin, Its Practical Application, 2d ed., Butterworth & Co., Ltd., London, 1950.

[67] Cf. U. S. Department of Agriculture, Yearbook of Agriculture, 1950–51, "Glossary," p. 917: "Titer or Titre * * * (1) The strength of a solution, or the concentration of a substance in solution, as determined by titration or by microbiological assay; * * *."

It is difficult to know what was the concentration, expressed in modern international units, of Fleming's original liquid preparation, but most estimates make it highly probable that it contained no more than 2 or 3 units, that is, 1 to 2 micrograms, per milliliter. In the early days of penicillin production by surface fermentation this was pushed up to 10, 20, or even 30 micrograms, which was considered by those working in the field under wartime conditions to be a pretty remarkable achievement. Then came further technological improvements, as well as the successful search for strains of higher penicillin-producing capacity, and the titers went up to 60 or 70 micrograms or more.

* * * * * * *

Production on what was then thought to be the "large scale" was by surface culture in unit vessels. Their size was restricted by the nature of the strains used, which could not feed economically on layers of medium more than a few centimeters deep. Tray culture was never successfully exploited, owing, as we now know, to the inevitably increased difficulty of avoiding bacterial contamination over large surfaces. * * *[68]

Apart from general increases in knowledge concerning the nutritive requirements of the penicillin strains in use, and minor technical improvements in the handling of the mold and its metabolite, including greater efficiency in extracting the penicillin from the fermentation liquors, there was one outstanding discovery made at the United States Department of Agriculture, Northern Regional Research Laboratory, at Peoria, responsible for a greater step-up of *titer* than almost all other improvements put together. This was the finding that washings from the maize starch industry * * * contained a stimulant not only for the growth of penicillium, but also for the production of penicillin—and these are not necessarily the same thing. These washings, when concentrated, were an agricultural byproduct known in the United States as corn steep liquor * * *. Much credit for this advance must go to Dr. R. D. Coghill, who was in charge of penicillin research at Peoria. Whatever the origins of the finding, it has led, as a byproduct, to a marked step-up in penicillin production. * * *

* * * * * * *

Neither the experts in Dr. Coghill's team at Peoria nor the several industrial and academic groups working on penicillin in this country and the United States were content to let the matter rest at the stage when corn steep liquor was being fully exploited for its beneficent effect on penicillin production. The goal of submerged culture, which would allow the replacement of small fermentation units in large numbers by large units in small numbers, was always before their eyes and in their minds. The exploitation of such strains, it was then discovered, would have to await solution of the complex and novel problems in chemical engineering presented by the need to carry out aerobic fermentation in large vessels of 5,000 gallons or more, with continuous agitation and under entirely aseptic conditions. This problem, which was handed by common consent to our wartime American colleagues in the field, and was brilliantly solved by United States chemical engineers, was followed by the erection of plant on both sides of the Atlantic capable of using the recently discovered varieties of penicillium that would grow beneath the surface and subsequently of improved strains that were the result of deliberate attempts to produce mutations by irradiation and other standard procedures. The experimental work that led, and is

[68] "Penicillin Production, 1929–54," The Practitioner, vol. 174, January 1955, pp. 9–10.

> still leading, to the upgrading of the molds and other organisms that produce antibiotics has yielded rich harvests; today, titres 50 to 100 times those achieved in the early days of surface culture are normal on both sides of the Atlantic.[69]

Bachrach summarized briefly "the historical succession of four stages between the discovery of penicillin" and 1955, when the article was written. Slightly paraphrasing his language, these stages are: first, "the work of Fleming on its biological properties and the initial studies by Raistrick and his colleagues of its chemistry and the means to purify it"; second, "the brilliant and arduous work of Florey and his colleagues at Oxford, which not only made it desirable to produce penicillin on a large scale, but also gave many valuable pointers to the means of doing it"; next "a period of building up the new antibiotic industry, under wartime conditions, on the basis of surface culture, aided by the use of corn steep liquor and various other devices for raising titres"; and "the last phase, in which we still are, * * * that due to the use of surface-growing strains, and their continued upgrading, in deep fermenters."

Regarding the broad significance of these developments, he concluded his paper with the following statement:

> It is perhaps worth pointing out that these advances did something more than improve penicillin production. They made available not only plant but also "know-how" about aerobic asceptic fermentation on a manufacturing scale for submerged culture, so that the problems of producing on a similar scale further antibiotics, as they were discovered and became of practical interest to the medical profession, were half solved before they were even posited. And this applies not only to antibiotic production, but also to the manufacture of at least one other compound of wide medical importance, namely, cyanocobalamin (vitamin B_{12}), as well as to operations needed during the manufacture of riboflavine. * * *[70]

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[69] *Ibid.*, pp. 10–11.
[70] *Ibid.*, p. 11.

APPENDIX III

Table of Conversion Ratios for Chapter III

APPENDIX TABLE FOR CHAPTER III

Rates used in converting to pounds in tables 8 and 9

Generic name	Billion units per pound
Penicillin:	
Triethylamine	0.70
Calcium	.75
Potassium	.72
Sodium	.755
Procaine	.457
Aluminum	.498
Ephedrine	.539
Dibenzylethylenediamine	.548
I-Ephenamine	.479
"O" Potassium	.734
Benzathine	.548
Chloroprocaine Penicillin "O"	.434
"V"	.767
"V" Benzathine	.767
"V" Potassium	.767
"V" Hydrabamine	.767
"O" Sodium	.755
Bacitracin	.0226
Nystatin	1.58
Polymyxin	2.812
	Kilograms per pound
Streptomycin, dihydrostreptomycin, neomycin, chlortetracycline, chloramphenicol, tyrothrycin, oxytetracycline, viomycin, actidione, erythromycin, fumagillin, carbomycin, tetracycline, anisomycin, cycloserine, amphomycin, novobiocin, oleandomycin, and candicidin	0.4536

Source: D. C. Grove and W. A. Randall, Assay Methods of Antibiotics, Medical Encyclopedia Inc., New York, 1955; Federal Register December 20, 1955; p. 9669, Webster's New Collegiate Dictionary, 1956, p. 970; Jawetz, Ernest, "Polymyxin, Neomycin, Bacitracin, Antibiotics," Monograph No. 5, Medical Encyclopedia Inc., New York, 1956, p. 51; FTC manufacturers' estimates.

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APPENDIX IV

Legal Documents

Exhibit 1

Dihydrostreptomycin Licensing Agreement of March 22, 1948, entered into as of March 22, 1948, by and between Merck & Co., Inc., a New Jersey corporation having its principal office at Rahway, N. J. (hereinafter referred to as "Merck"); Parke, Davis & Co., a Michigan corporation having its principal office at Detroit 32, Mich. (hereinafter referred to as "Parke"); E. R. Squibb & Sons, a New York corporation having its principal office at 745 Fifth Avenue, New York 22, N. Y. (hereinafter referred to as "Squibb").

Witnesseth:

Whereas each party represents that it owns the entire right, title, and interest in and to one of the applications involved in Interference No. 83,055 and set forth in schedule A, attached hereto;

Whereas said interference and other interferences closely allied with Interference No. 83,055 as may occur by reason of motions under rule 109 would entail expense and protracted delay to determine to which party or parties patents should be issued, and each party is desirous of eliminating or reducing such expense and delay; and

Whereas each of the parties represents that it has full power to enter into and carry out the terms of this agreement;

Now, therefore, in consideration of the premises and of the mutual covenants hereinafter contained, it is hereby mutually agreed as follows:

ARTICLE I: DEFINITIONS

A. The term "United States," as used in this agreement, shall mean the territory, including the United States of America proper and Puerto Rico, in which United States patents are effective.

B. The term "licensed matter," as used in this agreement, shall mean: (1) the counts of Interference No. 83,055 as originally declared; (2) any additional counts of Interference No. 83,055; (3) any counts of any other interference between applications owned by two or more of the parties hereto arising out of motions under rule 109 in Interference No. 83,055, where such counts of the other interference are directed to dihydrostreptomycin or the production thereof, and are in accord with the provisions of the last sentence of this paragraph B; and (4) any claim of any application owned by any party hereto where such claim, otherwise allowable, has been stated by the Patent Office to be held subject to the determination of Interference No. 83,055. In no event shall licensed matter be understood to extend to claims to any part or all of any process for producing streptomycin per se or any salt thereof, or to any compound or intermediate prepared in or resulting from such production.

C. The term "licensed patent," as used in this agreement, shall mean any patent granted on any application of any party hereto containing as a claim therein any licensed matter, or any reissue of such patent.

D. The term "net selling price," as used in this agreement, shall mean, as to products on which royalty is payable by virtue of article IV hereof, the seller's wholesale price f. o. b. place of manufacture, minus:

(1) Transportation charges or allowances (for the delivery of such products from the f. o. b. place of manufacture to the customer), if any, paid or allowed by the seller;

(2) Trade discounts and/or quantity discounts allowed, if any;

(3) Cash discount of 2 percent, whether allowed or not;

(4) Sales and other excise taxes and duties imposed upon and paid by the seller directly with respect to the sale; and

(5) Allowances or credits to customers on account of settlement of complaints, rejection or return of such products, or retroactive price reductions.

For the purposes of this agreement, a product shall be considered as sold when shipment thereof is made by a licensed party to its customer.

E. The term "subsidiary," as used in this agreement, shall mean any corporation of whose voting stock one of the parties hereto owns at the time at least a majority, such corporation being deemed a subsidiary only as long as such ownership continues.

ARTICLE II: SETTLEMENT OF INTERFERENCES

A. The parties hereto shall settle, as rapidly and efficiently as possible and in accordance with the provisions of paragraphs B and C of this article, the controversy regarding priority of invention as to any licensed matter.

B. Within a reasonable time after the receipt of a completely executed copy of this agreement, and within a reasonable time after the declaration of any subsequent interference among parties hereto concerning licensed matter, the parties hereto shall, through their patent attorneys, confer on the question of priority with respect to any claims of applications involved in said interferences and grant concessions of priority, or abandonments of the contest, if they can agree as to priority.

C. Where there is doubt as to which party is entitled to priority, the parties, through their patent attorneys, shall stipulate evidence, and such evidence shall be submitted to the Patent Office in accordance with the rules thereof. Each party shall assist in the rapid determination of priority by the use of such stipulations to as great an extent as its patent attorney may deem to be non-prejudicial. Any party may supplement such stipulations, if desired, by testimony not inconsistent therewith and in accordance with the rules of the Patent Office. Such stipulations, so supplemented, shall constitute the records of the parties in said interferences. The decision of the Board of Interference Examiners, based on such records, shall be accepted as final and conclusive upon each of the parties hereto, and each such party hereby waives any and all right to appeal from any such decision; provided, however, that the parties hereto may take any or all appellate or other procedures against strangers to this agreement.

ARTICLE III: GRANT OF LICENSE

A. Each of the parties hereto hereby grants each of the other parties a non-exclusive license under all licensed patents owned by such granting party to make, use and sell any product covered by, and to practice any process covered by, any claim of such patent within the scope of the licensed matter. To the extent necessary to render operative the licenses herein granted, they shall be construed as extending to claims of patents owned or controlled by the granting parties which claim or claims in respect of dihydrostreptomycin or the production thereof are broader than the licensed matter (and so dominate the licensed matter) and are necessarily infringed by practicing a process or preparing a product under such licenses; but in no event shall this extenison to such dominating claims be understood to apply to claims to any part or all of any process

for producing streptomycin per se or any salt thereof, or to any compound or intermediate prepared in or resulting from such production. These licenses are subject to the royalty provisions of article IV.

B. The licenses granted pursuant to this article III affect only United States patents, relate only to activities within the United Sates and do not carry with them any license, express or implied, under any patent of any party, except as in this agreement expressly provided.

ARTICLE IV: ROYALTIES

A. Royalty, as set forth in detail in paragraph B of this article IV, is payable with respect to operations under a licensed patent, and it is contemplated in such paragraph B that if all or part of the licensed matter shall appear as claims in any patent or patents owned by one party, none of the remainder, if any, of such licensed matter shall appear as a claim in any patent owned by another party. In other words, it is contemplated in such paragraph B that one party shall prevail over the other two parties as to all licensed matter granted in any patent. Thus, royalty with respect to licensed operations shall be payable by each of the two losing parties to the prevailing party.

B. Any party hereto operating under a licensed patent or patents shall pay to the owner thereof a royalty of one percent (1%) of the net selling price of all quantities of any product (1) sold by such operating party and covered by any claim of such patent or patents that is within the scope of the licensed matter; or (2) made by a process covered by any claim of such patent or patents that is within the scope of the licensed matter and sold by such operating party. If such operating party uses any such product during any given period in the production of other materials, the product so used, and not such materials, shall be subject to royalties hereunder when such materials shall have been sold by such operating party; and the net selling price of the product so used shall be based on the amount which such operating party would have received from the sale of the used quantity of such product per se at such party's regular published price therefor during said period. If there is no such price, such basis shall be the then-current price therefor on the open market.

C. If, however, one of the parties hereto prevails over the others as to one part of the licensed matter and another party prevails as to a different part thereof, so that such parts shall appear as claims of diversely owned patents, the parties hereto agree to negotiate a mutually satisfactory adjustment of royalties payable by parties operating under such claims, such adjustment to reflect the relative importance of the claims concerned. In no event shall a party hereto pay royalties aggregating more than one percent (1%), computed in accordance with paragraph B of this article IV, with respect to any product on which royalties are payable. If the parties concerned are unable to agree on such adjustment, the matter shall be arbitrated as provided in article VIII hereof.

D. If there should be marketed in substantial quantity by a stranger to this agreement a product covered by, or made by a process covered by, a claim of any licensed patent within the scope of the licensed matter, and such stranger is not licensed under such licensed patent, no royalty shall be payable by any party with respect to its operations under such licensed patent while such marketing continues.

E. Each party operating under any claim of any licensed patent coming within the scope of the term licensed matter, agrees to render to the owner of such patent a written report within two (2) months after the end of each calendar half-year, stating that party's operations under such license to an extent sufficient to show the royalty due for such operations during such calendar half-

year, and, simultaneously therewith, to pay the royalties shown due thereon as provided in this article IV. Each such party agrees to keep full, true, and exact records of all its operations under the license involved, in sufficient detail to enable the royalty payable by such party to be determined, and further, to permit its books and records to be examined, not oftener than once annually, to the extent necessary to verify such reports. Such examination may be made at the expense of the party owning the licensed patent, by any auditor appointed by such party and acceptable to the party making royalty payments, or by a certified public accountant appointed by the party owning the licensed patent, or, at the option and expense of the party making the royalty payments, by independent certified public accountants selected by such party making the royalty payments. In no event are the quantities or prices to individual customers, or costs of production, to be disclosed to the party owning the licensed patent.

F. If a product is covered, or made by a process covered, only by a claim held invalid in an unappealed or unappealable decision of a court of competent jurisdiction, no royalty shall be payable with respect to the manufacture, use and/or sale of such product after the date of such decision.

ARTICLE V: TERM OF LICENSES

Licenses herein granted are to extend for the full life of the patents licensed, subject, however, to termination as provided for in article VI hereof.

ARTICLE VI: TERMINATION OF LICENSES

Licenses herein granted are terminable forthwith by the granting party upon written notice to the party licensed who (1) after preliminary written notice to pay royalties due to such granting party, fails to pay such royalties within sixty (60) days after such preliminary notice, or (2) in case a controversy regarding such royalties has developed, fails to pay within sixty (60) days after the date set in a decision under article VIII hereof requiring that royalty be paid, or (3) becomes insolvent or makes an assignment for the benefit of creditors. In the event of such termination, unpaid royalties accrued to the effective date thereof shall be payable forthwith.

ARTICLE VII: LICENSES TO STRANGERS

In the event that any party hereto should grant to any stranger to this agreement a license, under any of the licensed patents, of the same scope as the licenses granted hereunder and at a lower royalty rate than provided for in article IV hereof (excepting licenses the consideration for which consists in whole or in part of patent rights or other rights of such substantial value as in the opinion of such party are sufficient to warrant a reduction in royalty rate below that provided for hereunder, or the acceptance of such rights in lieu of royalties), such party shall promptly give the other parties hereto notice thereof, and such other parties shall have the right to amend the royalty rate provided for in article IV hereof to conform to such lower royalty rate, such amendment to be effective as of the effective date of such license to such stranger and for as long as such lower royalty rate is available to such stranger.

ARTICLE VIII: ARBITRATION

This agreement shall be construed in accordance with the law of the State of New York. Controversies of any kind relating to this agreement, other than those referred to in article II hereof, shall, at the option of any party involved in such controversies, be settled by arbitration in accordance with the rules then obtaining of the American Arbitration Association. All the parties thereto

agree to be bound by the decision in any such arbitration, and agree that judgment upon such decision may be entered in any Federal or State court having jurisdiction.

ARTICLE IX: COVENANTS OF FURTHER ASSURANCE

Each party agrees, upon request of any other party hereto, to execute such documents and take such action as may reasonably be required in order to carry out the intents and purposes of this agreement.

ARTICLE X: NOTICES

Any notice required or permitted to be given under this agreement by any of the parties to any of the others shall be deemed to have been sufficiently given for all the purposes hereof if mailed by registered mail, postage prepaid, addressed to the party to be notified at its address shown at the beginning of this agreement or at such other address as it may have theretofore furnished in writing to the notifying party.

ARTICLE XI: ASSIGNABILITY

This agreement shall inure to the benefit of subsidiaries and successors of the parties hereto or to an assignee of all or substantially all of the business and assets pertaining to the antibiotic business of a party, but shall otherwise be assignable only after prior written consent of all the other parties. Each party shall remain liable for the performance of its obligations hereunder as respects the activities of its subsidiaries.

In witness whereof, each party has caused its corporate signature and seal to be affixed and attested by its duly authorized officers, as of the date first above written.

MERCK & CO., INC.,
By ——— ———,
Vice President.

Attest:
——— ———,
Secretary.

PARKE, DAVIS & CO.,
By ——— ———,
Vice President.

Attest:
——— ———,
Secretary.

E. R. SQUIBB & SONS,
By ——— ———,
Vice President.

Attest:
——— ———,
Secretary.

SCHEDULE "A"

1. Owned by Merck & Co., Inc.
   Application of Robert L. Peck, Serial No. 648,007; filed February 15, 1946.
2. Owned by Parke, Davis & Co.
   Application of Mildred C. Rebstock and Harry M. Crooks, Jr., Serial No. 671,122; filed May 20, 1946.
3. Owned by E. R. Squibb & Sons.
   Application of Josef Fried and Oskar Wintersteiner, Serial No. 668,482; filed May 9, 1946.

Exhibit 2

Rejection of Tetracycline Patent Application
(Mailed November 24, 1954)

Department of Commerce

UNITED STATES PATENT OFFICE

Washington

Connolly and Hutz, 228 Delaware Trust Bldg., Wilmington 1, Del.

Paper No. 10

Applicant: Lloyd H. Conover

Ser. No. 385,041

Filed Oct. 9, 1953. Mailed Nov. 24, 1954, Pat. Div. 6

FOR TETRACYCLINE

Please find below a communication from the examiner in charge of this application.

(s) Robert C. Watson,
Commissioner of Patents.

Art cited:
Duggar, 2,482,055, Sept. 13, 1949, 260/559.
Niedercorn, 2,609,329, Sept. 2, 1952, 260/559.

Interference No. 86,861 having been dissolved and Interference No. 86,799 having terminated favorable to applicant, ex parte prosecution is resumed.

Claims 7, 8 and 9 are allowed.

All the product claims, 1 to 6, are rejected as being unpatentable over each of Duggar and Niedercorn for the reasons set forth in the Examiner's Motion to Dissolve (XII) in Interference No. 86,861 and repeated below:

The product claims are unpatentable over the disclosures of Duggar U. S. 2,482,055, September 13, 1949, and Niedercorn, U. S. 2,609,329, September 2, 1952. Duggar and Niedercorn each produce an antibiotic, disclosed as "Aureomycin" by a fermentation process employing *Streptomyces aureofaciens* and mutants thereof. The antibiotic is identified as an antibiotic by assay against bacteria. It appears from the disclosure of Minieri et al. (a party to Interference No. 86,861 in an application available to all the parties, that tetracycline is *also* produced in such a fermentation process and that larger proportions thereof are produced when the amount of chloride in the fermentation medium is low (see p. 1, lines 5 to 20 and lines 24 to 28, and pp. 12, 16, 17, 18, and 19 of Minieri et al. S. N. 382,637). Minierie et al. clearly and specifically disclose that the micro-organism used to prepare *tetracycline* belongs to the Duggar et al. U. S. 2,482,055 species and that "the characteristics are identical with those exhibited by a known culture of S. *aureofaciens*." While neither Duggar nor Niedercorn may have realized that tetracycline was in fact produced, they did appreciate and disclose, that the product was an antibiotic. No invention is involved in the *identification* of the tetracycline and its hydrochloride inherently produced by the reference processes. (See *In re Lieser*, 1947, C. D. 447, and *Allen et al.* v. *Coe*, 1943, C. D. 55.) It has long been held that a purer form of an old product is not inventive and the (apparent) mixture of the prior art meets the claims. (See *Parke, Davis* v. *Mulford*, 189 F. 95, and *In re Kebrich*, 96 USPQ 411.)

(Signed) ——— ———,
Examiner.

Lidoff: cln.